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(54) Title: DESLEUCYL GLYCOPEPTIDE ANTIBIOTICS AND METHODS OF MAKING SAME

(57) Abstract

Compounds that are analogs of glycopeptide antibiotics are disclosed. The compounds have the formula A_1–A_2–A_3–A_4–A_5–A_6–A_7 wherein each of the groups A_2 to A_7 is a modified or unmodified α–amino acid residue, A_1 is optional and, when present, is an organic group other than N–substituted leucine, and at least one of the groups A_1 to A_7 is linked via a glycosidic bond to one or more glycosidic groups each having one or more sugar residues, wherein at least one of said sugar residues is modified to bear at least one hydrophobic substituent. Methods of making these compounds, compositions including these compounds, and methods of using the compounds to treat infections in a host are also disclosed.

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DESLEUCYL GLYCOPEPTIDE ANTIBIOTICS AND METHODS OF MAKING SAME

BACKGROUND OF THE INVENTION

Field of the Invention

The present invention relates to glycopeptide compounds having antibiotic activity, and methods of making glycopeptide compounds having antibiotic activity.

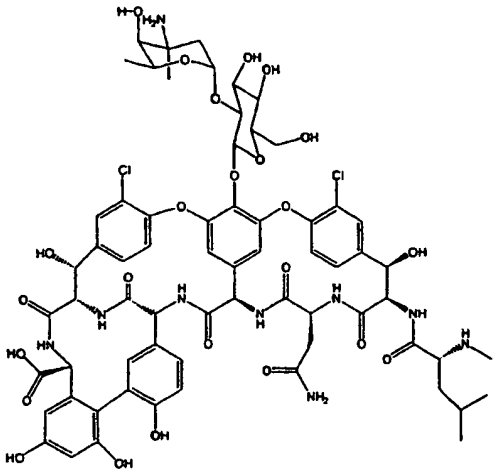
Background of the Invention

Glycopeptide antibiotics are characterized by having at least one saccharide group chemically bonded to a rigid peptide structure having a cavity or cleft which acts as a binding site for the substrate used in bacterial cell wall synthesis. The glycopeptide antibiotics are further categorized into various subclasses depending on the identity and interconnections of the amino acids comprising the peptide backbone and the number and substitution pattern of the sugar residues in the molecule. The glycopeptide antibiotics are generally active against Gram-positive bacteria but relatively ineffective against Gram-negative bacteria. Most notable among the glycopeptide antibiotics is vancomycin. Vancomycin is produced by *Amycolatopsis orientalis*, and is often referred to as "the drug of last resort" because it is effective against most multi-drug-resistant gram positive bacteria. However, in recent years, vancomycin-resistant strains of some bacteria have emerged.

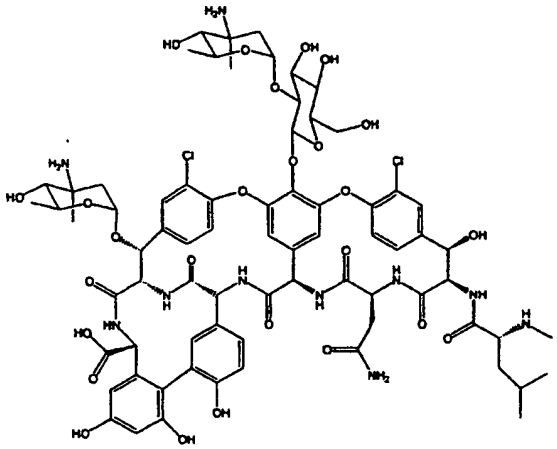
The structural formula of vancomycin is shown below and is characterized by a disaccharide moiety covalently linked to a heptapeptide structure. The structure of vancomycin places it in a class of molecules referred to as the "dalbaheptides." [Malabarba A., et al. (1997a)]. Dalbaheptides in general are characterized by the presence of seven amino acids linked together

by peptide bonds and held in a rigid conformation by cross-links through the aromatic substituent groups of at least five of the amino acid residues. In the heptapeptide structure of vancomycin, which is commonly referred to as the "aglycone" of vancomycin, the aromatic side-chains of amino acids 2, 4, and 6 are fused together through ether linkages. The aromatic side-chains of amino acids 5 and 7 are joined via a carbon-carbon bond. Amino acids 1 and 3 are N-methyl leucine and asparagine, respectively. Other naturally-occurring glycopeptide antibiotics are similar to vancomycin in that they have the same amino acids 1 through 7 forming the peptide binding pocket and a glucose residue linked to the aromatic substituent on amino acid 4 through formation of a bond with a phenolic hydroxyl group. The glucose residue, in turn, is linked through its vicinal hydroxyl position to a unique amino sugar, L-vancosamine. Some glycopeptide antibiotics similar to vancomycin contain additional glycosidic groups attached to other positions on the peptide (e.g. chloroeremomycin). Still other glycopeptide antibiotics such as β-avoparcin are similar to vancomycin in that they contain the same amino acids at all positions except positions one and three. β-avoparcin, for example, contains an amino acid containing an aromatic side chain in place of the asparagine at position three and does not contain N-methyl leucine at position one. β-avoparcin contains glycosidic groups at amino acid 4 and at other positions on the peptide core.

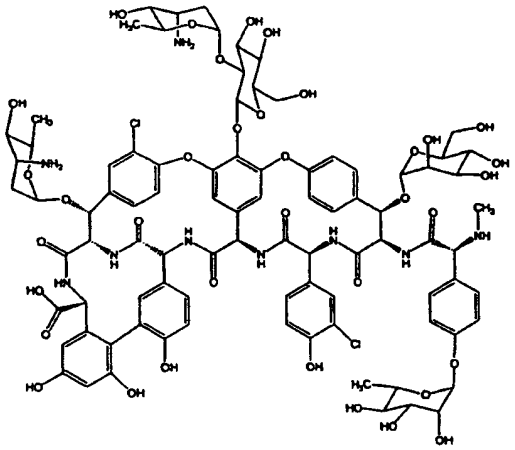
Vancomycin, chloroeremomycin and β-avoparcin have the structures as shown below:



Vancomycin



Chloroeremomycin



β-Avoparcin

Eremomycin has the structure of chloroeremomycin except that the chlorine substituent on the aromatic group attached to amino acid 6 is not present in eremomycin.

The anti-microbial activity of the naturally occurring glycopeptide antibiotics is believed to be due to their ability to interfere with biosynthesis of the bacterial cell wall, evidently by

binding to dipeptide termini of uncross-linked peptidoglycan and/or the disaccharide precursor of peptidoglycan. [Nagarajan R. (1993)]. NMR evidence has shown that the heptapeptide chain of vancomycin forms a number of hydrogen bonds with D-alanyl-D-alanine, the dipeptide that is at the terminus of the peptide chain attached to the N-acetylmuramic acid unit that is incorporated into peptidoglycan. [See, e.g., Prowse W., et al. (1995); Pierce C., et al. (1995); Williams D. et al. (1998)]. The interaction of vancomycin with peptidoglycan precursors apparently inhibits or prevents the subsequent transglycosylation and/or transpeptidation steps of cell wall assembly. Supporting this mode of action is the fact that vancomycin-resistant strains of bacteria are found to produce a pentapeptide precursor terminating in a D-alanyl-D-lactate sequence. It is hypothesized that the reduced effectiveness of vancomycin against resistant strains is due to reduced hydrogen bonding interactions between the drug and the D-alanyl-D-lactate substrate (and possibly repulsive interactions as well). The affinity of vancomycin for D-alanyl-D-lactate is estimated to be 2-3 orders of magnitude (4.1 kcal/mol) less than for D-alanyl-D-alanine. [Walsh C (1993)].

The sugar residues of vancomycin and other glycopeptide antibiotics have been shown to affect biological activities. Structural changes in the sugar residues can produce significant changes in antibiotic activity. [Malabarba (1997); Nagarajan, R. (1993)]. It has been proposed that the sugar residues on the glycopeptide antibiotics may enhance the avidity of these molecules for surface-bound peptide ligands. At least two different mechanisms for enhancing avidity have been proposed. [Kannan (1998); Gerhard (1993); Allen (1997)].

For example, it has been proposed that the biological activity of vancomycin, along with that of many other glycopeptide antibiotics, is enhanced by dimerization [Williams D., et al. (1993); Gerhard U., et al., (1993)] facilitated by the saccharide groups on the convex surface of

the molecules. Structural evidence for dimerization of several different glycopeptides has been obtained from both NMR and crystallographic studies. It has been found that there are significant differences in the stability of the dimers formed in solution by different glycopeptide antibiotics. [MacKay (1994)]. Dimerization is thought to influence activity by increasing the avidity of the glycopeptides for surface-bound D-ala-D-ala peptide ligands [Williams, (1998)]. It is proposed that the differences in the dimerization constants, due to different interactions between saccharide groups, may account at least partially for the differences in biological activity of different glycopeptide antibiotics which otherwise have very similar peptide binding pockets and also have similar affinities for the natural D-ala-D-ala substrate. [Williams (1998)].

A second mechanism for enhancing activity has been proposed for the naturally occurring glycopeptide antibiotic teicoplanin and various semi-synthetic glycopeptides containing hydrophobic substituents on at least one of the saccharide units. It is suggested that hydrophobic substituents (a C2 N-acyl group in the case of teicoplanin) interact with the bacterial membrane, thus "anchoring" hydrophobically substituted glycopeptides at the membrane surface. [Beauregard (1995)]. Membrane anchoring is proposed to enhance activity by localizing the glycopeptide antibiotic to the membrane where the Lipid II substrates that are the precursors of peptidoglycan are found. The glycopeptide antibiotics then bind to the dipeptide termini of these precursors and prevent transglycosylation and/or transpeptidation.

It should be noted that teicoplanin is active against some vancomycin resistant strains. Furthermore, the attachment of hydrophobic substituents to the vancomycin carbohydrate moiety confers activity against these and other vancomycin-resistant bacterial strains. [Nagarajan (1991)]. It has been speculated that the lipophilic groups on the saccharides, in locating the antibiotic at the cell surface, help overcome the decreased binding affinity for D-ala-D-lac in

vancomycin resistant microorganisms.

It has generally been assumed that peptide binding is essential for biological activity. In fact, it had been shown that if the peptide core of vancomycin is damaged by removing the N-methyl leucine (amino acid 1), the resulting compound loses affinity for D-ala-D-ala and has no biological activity, even against sensitive bacterial strains. The lack of biological activity is presumed to be due to the inability of the compound to bind D-Ala-D-Ala well.

Previously, others have explored the possibility of attaching amino acids other than N-methyl leucine to the amino acid 2 on des-N-methyl leucyl vancomycin. It was found that some amino acid substitutions produced compounds with comparable activity to vancomycin; some had worse activity. No useful improvements in activity have been reported. As far as we know, no substitutions have ever been made at the A_1 position of any dalbaheptides wherein A_1 and A_3 are not directly linked by a covalent bond and wherein there is at least one hydrophobic substituent on at least one of the sugar moieties attached to at least one of the amino acids A_2-A_7. Thus, replacing N-methyl leucine at A_1 on vancomycin with other amino acids did not yield any compounds having significantly better properties than vancomycin itself. Hence, it would not be expected that glycopeptides having at least one hydrophobic substituent attached to a glycosidic group on any one of amino acids A_2-A_7 and having no A_1 group or an A_1 group other than an N-substituted leucine would have any antibiotic properties, much less better antibiotic properties than the precursor glycopeptide compounds.

Definitions

A "glycoconjugate" comprises any molecule linked to at least one carbohydrate of any size. The molecule can be a peptide or protein, a nucleic acid, a small molecule, a lipid, or another carbohydrate; it may be of natural or non-natural origin.

A "glycopeptide" is a glycoconjugate comprising a peptide linked to at least one carbohydrate.

A "glycopeptide antibiotic" is a glycopeptide having antibacterial activity, including, e.g., vancomycin, eremomycin, chloroeremomycin and β-avoparcin as well as any synthetic and semi-synthetic derivatives thereof. The term "glycopeptide antibiotic" is meant to encompass any naturally occurring antibiotic as well semi-synthetic derivatives thereof.

An "aglycone" is the result of removing the carbohydrate residues from a glycopeptide, leaving only a peptide core.

A "des-N-methyl leucyl aglycone" is the result of removing a terminal N-methyl leucine residue from an aglycone.

A "pseudoaglycone" is the result of removing only one of two sugar residues from a disaccharide residue linked to amino acid residue A_4 of a glycopeptide. Thus, a pseudoaglycone comprises an aglycone in which A_4 is linked to a monosaccharide residue.

A "des-N-methyl leucyl pseudoaglycone" is the result of removing a terminal N-methyl leucine residue from an pseudoaglycone. Thus, a des-N-methyl-leucyl pseudoaglycone is an aglycone in which A_4 is linked to a monosaccharide residue and which has a terminal N-methyl leucine residue removed therefrom.

A "dalbaheptide" is a glycopeptide containing a heptapeptide moiety which is held in a rigid conformation by cross-links between the aromatic substituent groups of at least five of the seven α-amino acid residues, including a cross-link comprising a direct carbon-carbon bond between the aryl substituents of amino acid residues 5 and 7, and aryl ether cross-links between the substituents of amino acid residues 2 and 4, and 4 and 6. Amino acid residues 2 and 4-7 in different dalbaheptides are those found in the naturally occurring glycopeptide antibiotics. These

amino acid residues differ only in that residues 2 and 6 do not always have a chlorine substituent on their aromatic rings, and in that substitution on free hydroxyl or amino groups may be present. Amino acids residues 1 and 3 may differ substantially in different dalbaheptides; if both bear aryl substituents, these may be cross-linked. Molecules having a dalbaheptide structure include, e.g., the glycopeptide antibiotics mentioned above.

The term "alkyl" refers to a linear or branched acyclic or non-aromatic cyclic group having form one to twenty carbon atoms connected by single or multiple bonds. Thus, the term "alkyl" is meant to encompass linear or branched acyclic or non-aromatic groups having one or more carbon-carbon double or triple bonds, i.e., alkenyl and alkynyl groups. An alkyl group may be substituted by one or more of halo, hydroxyl, protected hydroxyl, amino, protected amino, nitro, cyano, alkoxy, aryloxy, aralkyloxy, COOH, aroyloxy, alkylamino, dialkylamino, trialkylammonium, alkylthio, arylthio, alkanoyl, alkanoyloxy, alkanoylamido, alkylsulfonyl, arylsulfonyl, aroyl, aralkanoyl, heterocyclic, $CONH_2$, CONH-alkyl, $CON(alkyl)_2$, COO-aralkyl, COO-aryl or COO-alkyl.

The term "aryl" refers to a group derived from a non-heterocyclic aromatic compound having from six to twenty carbon atoms and from one to four rings which may be fused or connected by single bonds. An aryl group may be substituted by one or more of alkyl, aralkyl, heterocyclic, heterocyclic-alkyl, heterocyclic-carbonyl, halo, hydroxyl, protected hydroxyl, amino, protected amino, hydrazino, alkylhydrazino, nitro, cyano, alkoxy, aryloxy, aralkyloxy, aroyloxy, alkylamino, dialkylamino, trialkylammonium, alkylthio, arylthio, alkanoyl, alkanoyloxy, alkanoylamido, alkylsulfonyl, arylsulfonyl, aroyl, aralkanoyl, COO-alkyl, COO-aralkyl, COO-aryl, $CONH_2$, CONH-alkyl or $CON(alkyl)_2$.

The term "aralkyl" refers to an alkyl group substituted by an aryl group. Aralkyl may

optionally be substituted with one or more of the groups with which alkyl or aryl may be substituted.

The term "heterocyclic" refers to a group derived from a heterocyclic compound having from one to four rings, which may be fused or connected by single bonds; said compound having from three to twenty ring atoms which may be carbon, nitrogen, oxygen, sulfur or phosphorus. A heterocyclic group may be substituted by one or more alkyl, aryl, aralkyl, halo, hydroxyl, protected hydroxyl, amino, hydrazino, alkylhydrazino, arylhydrazino, nitro, cyano, alkoxy, aryloxy, aralkyloxy, aroyloxy, alkylamino, dialkylamino, trialkylamino, alkylthio, arylthio, alkanoyl, alkanoyloxy, alkanoylamido, alkylsulfonyl, arylsulfonyl, aroyl, aralkanoyl, COO-alkyl, COO-aralkyl, COO-aryl, $CONH_2$, CONH-alkyl or $CON(alkyl)_2$.

The terms "alkoxy," "aryloxy," and "aralkyloxy," refer to groups derived from bonding an oxygen atom to an alkyl, aryl or aralkyl group, respectively. Any alkoxy, aryloxy or aralkyloxy group may optionally be substituted with one or more of the groups with which alkyl, aryl or aralkyl may be substituted. The terms "alkanoyl," "aroyl," and "aralkanoyl" refer to groups derived from bonding a carbonyl to an alkyl, aryl or aralkyl group, respectively. Any alkanoyl, aroyl or aralkanoyl group may optionally be substituted with one or more of the groups with which alkyl, aryl or aralkyl may be substituted. The terms "heterocyclic-alkyl" and "heterocyclic-carbonyl" refer to groups derived from bonding a heterocyclic group to an alkyl or a carbonyl group, respectively. An heterocyclic-alkyl or heterocyclic-carbonyl group may optionally be substituted with one or more of the groups with which heterocyclic or alkyl may be substituted. The term "heterocyclic-alkyl-carbonyl" refers to a group derived from bonding a heterocyclic-alkyl group to a carbonyl group. Any heterocyclic-alkyl-carbonyl may optionally be substituted with one or more of the groups with which heterocyclic or alkyl may be substituted.

The term "alkylsulfonyl" refers to a group derived from bonding an alkyl group to a sulfonyl group. An alkylsulfonyl group may optionally be substituted with one or more groups with which alkyl may be substituted. The term "arylsulfonyl" refers to a group derived from bonding an aryl group to a sulfonyl group. An arylsulfonyl group may optionally be substituted with one or more groups with which aryl may be substituted. The term "protected hydroxyl" refers to a hydroxyl group bonded to a group which is easily removed to generate the free hydroxyl group by treatment with acid or base, by reduction or by exposure to light, or by any other conventional means for removing a protecting group from a hydroxyl group. The term "protected amino" refers to an amino group bonded to a group which is easily removed to generate the free amino group by treatment with acid or base, by reduction or exposure to light, or by any other conventional means for removing a protecting group from an amino group.

A "chemical library" is a synthesized set of compounds having different structures. The chemical library may be screened for biological activity to identify individual active compounds of interest.

The term "DMF" refers to N,N-dimethylformamide; "THF" refers to tetrahydrofuran; "TFA" refers to trifluoroacetic acid; "EtOAc" refers to ethyl acetate; "MeOH" refers to methanol, "MeCN" refers to acetonitrile; "Tf" refers to the trifluoroacetyl group; "DMSO" refers to dimethyl sulfoxide; "DIEA" refers to diisopropylethylamine; "All" in structural formulas refers to the allyl group; "Fmoc" refers to 9-fluorenylmethyloxycarbonyl; "HOBt" refers to 1-hydroxybenzotriazole and "Obt" to the 1-oxybenzotriazolyl group; "PyBOP" refers to benzotriazol-1-yl-oxyatripyrrolidine-phosphonium hexafluorophosphate; "Su" refers to the succinimidyl group; "HBTU" refers to O-benzoatriazol-1-yl-N2N3N',N'-tetramethyluronium hexafluorophosphate; "alloc" refers to allyloxycarbonyl; and "CBZ" refers to

benzyloxycarbonyloxy.

The term "hydrophobic" as used herein to describe a compound of the present invention or a substituent thereon, refers to the tendency of the compound or substituent thereon to lack an affinity for, to repel or to fail to absorb water, or to be immiscible in water. The term "hydrophobic" is not meant to exclude compounds or substituents thereon that are not completely immiscible in water.

The term "polar" as used herein to describe a compound of the present invention or a substituent thereon, refers to the tendency of the compound or substituent thereon to have an affinity for, to attract or to absorb water, or to be miscible in water. The term "polar" is not meant to exclude compounds or substituents thereon that are not completely miscible in water.

SUMMARY OF THE INVENTION

Thus, the present invention is directed to compounds of the formula A_1-A_2-A_3-A_4-A_5-A_6-A_7 wherein each of the groups A_2 to A_7 comprises a modified or unmodified α-amino acid residue, A_1 is optional and, when present, comprises an organic group other than N-substituted leucine, and at least one of the groups A_2 to A_7 is linked via a glycosidic bond to one or more glycosidic groups each having one or more sugar residues, wherein at least one of said sugar residues is modified to bear at least one hydrophobic substituent. In preferred compounds of the present invention, the glycosidic group is a disaccharide modified to bear at least one hydrophobic substituent. In a preferred embodiment of the present invention, each of the groups A_2, A_4, A_5, A_6 and A_7 bears an aromatic side chain and the aromatic side chains of groups A_2 and A_6 are linked to the aromatic side chain of group A_4 via ether linkages and the aromatic side chains of groups A_5 and A_7 are linked to each other via a carbon-carbon bond. In another preferred embodiment of the invention, the group A_4 bears a glycosidic group. The glycosidic

group is preferably is a disaccharide comprising a glucose residue directly bonded to group A_4 and a vancosamine residue bonded to said glucose residue. In preferred compounds of the present invention, A_2-A_3-A_4-A_5-A_6-A_7 is as found in a compound selected from the group consisting of vancomycin, eremomycin, chloroeremomycin, and β-avoparcin, more preferably A_2-A_3-A_4-A_5-A_6-A_7 is as found in vancomycin. In other preferred compounds of the present invention, the C_6 position of the glucose residue attached to A_4 is modified to bear at least one substituent other than hydroxyl, and more preferably the at least one substituent other than hydroxyl is a polar substituent or a hydrophobic substituent. In preferred compounds of the present invention where A_2-A_3-A_4-A_5-A_6-A_7 is as found in vancomycin, the vancosamine residue in vancomycin is N-substituted with said at least one hydrophobic substituent. In other preferred compounds of the present invention wherein A_2-A_3-A_4-A_5-A_6-A_7 is as found in vancomycin, the glucose residue attached to A_4 of vancomycin is modified at the C_6 position to bear at least one substituent other than hydroxyl, preferably a polar substituent, and said vancosamine residue is N-substituted with said at least one hydrophobic substituent. The at least one hydrophobic substituent is preferably selected from R, OR, NR_1R, SR, SO_2R, C(O)OR, C(O)SR, C(S)OR, C(S)SR, $NR_1C(O)R$, $C(O)NR_1R$, or halo and R is alkyl, aryl, aralkyl, alkanoyl, aroyl, aralkanoyl, heterocyclic, heterocyclic-carbonyl, heterocyclic-alkyl, heterocyclic-alkyl-carbonyl, alkylsulfonyl or arylsulfonyl; R_1 is hydrogen, alkyl, aryl, aralkyl, alkanoyl, aroyl, aralkanoyl, heterocyclic, heterocyclic-carbonyl, heterocyclic-alkyl, heterocyclic-alkyl-carbonyl, alkylsulfonyl or arylsulfonyl; and any pharmaceutically acceptable salts thereof; and if two or more of said substituents are present, they can be the same or different. The organic group A_1 in the preferred compounds of the present invention, is preferably an organic group selected from the group consisting of a modified or unmodified alpha amino acid residue other than N-substituted

leucine, alkyl, aryl, aralkyl, alkanoyl, aroyl, aralkanoyl, heterocyclic, heterocyclic-carbonyl, heterocyclic-alkyl, heterocyclic-alkyl-carbonyl, alkylsulfonyl, arylsulfonyl, guanidinyl, carbamoyl, or xanthyl. Also, in the preferred compounds of the present invention, the A_7 group bears a terminal carboxyl, ester, thioester, amide, N-substituted amide, or other carboxylic acid derivative, any of which groups may be substituted with any of the substituents described herein.

In another aspect, the present invention is also directed to a method for making compounds of the formula A_1-A_2-A_3-A_4-A_5-A_6-A_7 wherein each of the groups A_2 to A_7 comprises a modified or unmodified α-amino acid residue, A_1 comprises an organic group other than N-substituted leucine, and at least one of the groups A_1 to A_7 is linked via a glycosidic bond to one or more glycosidic groups each having one or more sugar residues, wherein at least one of said sugar residues is modified to bear at least one hydrophobic substituent comprising the steps of removing the N-substituted leucine residue from the compound N-substituted-leucyl-A_2-A_3-A_4-A_5-A_6-A_7 thereby forming a compound having a free amino group at A_2; and attaching an organic group A_1 to the free amino group at A_2, wherein the hydrophobic substituent and the groups A_1-A_7 are as described above. Preferably, the N-substituted-leucine residue is N-methyl leucine. This method is applicable to any of the preferred compounds as described above.

In another aspect, the present invention is directed to a method for making a glycopeptide antibiotic having the formula A_1-A_2-A_3-A_4-A_5-A_6-A_7 wherein A_2-A_3-A_4-A_5-A_6-A_7 is as found in vancomycin and A_1 comprises an organic group other than N-substituted leucine, said method comprising modifying vancomycin to form a modified vancomycin bearing a hydrophobic substituent at the vancosamine nitrogen; removing the N-methyl leucine residue from the modified vancomycin to form a des-N-methyl leucyl modified vancomycin bearing a free amino group at A_2 and attaching an organic group A_1 to the amino group at A_2, wherein the

hydrophobic substituent and the organic group A_1 are as defined above.

In another aspect, the present invention is directed to a method for making a glycopeptide antibiotic having the formula A_1-A_2-A_3-A_4-A_5-A_6-A_7 wherein A_2-A_3-A_4-A_5-A_6-A_7 is as found in vancomycin and A_1 comprises an organic group other than N-substituted leucine, said method comprising modifying vancomycin to form a first modified vancomycin bearing a substituent other than hydroxyl at the C_6 position of the glucose attached to A_4 of vancomycin; modifying said first modified vancomycin to form a second modified vancomycin bearing a hydrophobic substituent at the vancosamine nitrogen; removing the N-methyl leucine residue from said second modified vancomycin to form a des-N-methyl leucyl second modified vancomycin bearing a free amino group at A_2; and, attaching an organic group A_1 to the amino group at A_2, wherein the hydrophobic substituent and the organic group A_1 are as described above. It is preferred in this method that the substituent other than hydroxyl at the C_6 position of the glucose attached to A_4 of vancomycin is a polar substituent.

The present invention is also directed to a method of treating an infectious disease in a host comprising administering to said host an effective amount of a compound of the present invention, or a pharmaceutically acceptable salt or ester thereof. Preferably the host is a mammalian host, more preferably a human. The infectious disease is preferably a bacterial infection. The present invention is also directed to a composition comprising a compound of the present invention or a pharmaceutically acceptable salt or ester thereof and a pharmaceutically acceptable carrier or excipient. The compound of the present invention may be administered solely or in combination with any other drug or therapeutic agent.

The present invention is also directed to a method for removing an N-terminal amino acid residue from an oligopeptide or polypeptide comprising reacting an oligopeptide or a polypeptide

with phenylisothiocyanate in a pyridine-water-triethylamine solvent medium. Preferably, the reaction of the oligopeptide or polypeptide with phenylisothiocyanate is carried out in a 10:10:1 (volume) pyridine-water-triethylamine solvent medium. The reaction is preferably carried out at a temperature in the range of from 40-70 °C and for a period of time in the range of from 20 – 60 minutes. In preferred methods, the N-terminal amino acid residue is N-methyl leucine. The preferred oligopeptides are selected from the group consisting of a glycopeptide antibiotic, a pseudoaglycone and an aglycone, preferably a glycopeptide antibiotic or pseudoaglycone in which at least one of the glycosidic groups therein is modified to bear at least one hydrophobic substituent. Preferably, the glycopeptide antibiotic is vancomycin. More preferably, the disaccharide at A_4 of vancomycin is modified to bear at least one hydrophobic group. Preferably, the vancosamine nitrogen at A_4 of vancomycin is modified to bear at least one hydrophobic group. In preferred methods, the glucose residue attached directly to A_4 of vancomycin is modified to bear at least one substituent other than hydroxyl, which is preferably a polar substituent or a hydrophobic substituent. Where the glucose residue is modified to bear at least one substituent other than hydroxyl, it is preferred that the C_6 position of the glucose residue attached directly to A_4 of vancomycin is modified to bear a polar or a hydrophobic substituent.

DETAILED DESCRIPTION OF THE INVENTION

Herein we disclose strategies for finding promising glycopeptide compounds with good activity against sensitive and resistant bacterial strains. One strategy involves attaching substituents to the free amino group of amino acid 2 in des-N-substituted-leucine glycopeptides and analogs thereof containing at least one hydrophobic substituent on a glycosidic group attached to one of the amino acids A_2-A_7. We have also discovered that where at least one of the glycosidic groups attached to one of the amino acids A_2-A_7 bears a hydrophobic substituent,

it is not necessary to attach a group to the free amino group of amino acid A_2 upon removal of the N-substituted leucine residue in order to produce compounds having biological activity. Thus, we have found good activity in des-N-substituted leucine glycopeptide compounds in which at least one of the glycosidic groups attached to one of the amino acids A_2-A_7 bears a hydrophobic substituent and in which A_2 bears a free amino group upon removal of the N-substituted leucine residue therefrom. We have demonstrated the utility of the strategy by making a set of compounds, of which several have better activity against a range of strains than the corresponding compounds in which A_1 is N-substituted leucine, which is preferably N-methyl leucine. Some of the substitutions improve activity against both sensitive and resistant strains relative to N-methyl leucine; others improve activity more against sensitive strains than resistant strains; still other improve activity more against resistant strains than sensitive strains. Thus, it is possible to manipulate the biological activity in different ways by choosing appropriate A_1 substituents. It is also possible to manipulate the biological activity by choosing appropriate hydrophobic substituents. We also show that the physical properties of the compounds - e.g., the hydrophobic-hydrophilic balance as measured by HPLC retention times- are related to both the hydrophobic substituent, and when present, the specific group A_1. Having shown that both the physical properties and the biological activities of glycopeptide derivatives containing hydrophobic substituents on the sugars are affected by the identity of the hydrophobic substituent and, when present, the group A_1, the present invention is thus directed to all compounds of the general structure A_1-A_2-A_3-A_4-A_5-A_6-A_7 wherein the group A_1 is optional and, when present, is preferably an organic group having from 2-30 carbon atoms, which may contain heteroatoms. The organic group A_1 may contain more than 30 carbon atoms. The organic group A_1, when present, is attached to the amino group at A_2. The organic group A_1 may be linear, branched or

cyclic, or some combination thereof, and may include aliphatic, aromatic, and/or heterocyclic groups, provided that it is not a leucine or a modified leucine residue, and provided that it is not directly or indirectly linked by a covalent bond to amino acid 3. Preferably the organic group is a modified or unmodified alpha amino acid residue, alkyl, aryl, aralkyl, alkanoyl, aroyl, aralkanoyl, heterocyclic, heterocyclic-carbonyl, heterocyclic-alkyl, heterocyclic-alkyl-carbonyl, alkylsulfonyl, arylsulfonyl, guanidinyl, carbamoyl, or xanthyl.

When present, preferred A_1 groups are provided by the compounds listed in Table I following Example 3. The structural formulae of these preferred A_1 groups are also provided in Table I. These are merely preferred A_1 groups, and the present invention is not to be construed as being limited thereto. In general, A_1 can be any organic group that can be reacted with the free amino group at A_2 by, for example, formation of an amide linkage. Thus, preferred reagents which can be reacted with the free amino group at A_2 include compounds having a carboxylic acid group which reacts with the free amino group at A_2 to form the amide linkage. Such preferred compounds include those disclosed in Table I.

In preferred compounds of the present invention, each of the groups A_2 to A_7 comprises a modified of unmodified α-amino acid residue, whereby (i) the group A_1,when present, is linked to an amino group on the group A_2, (ii) each of the groups A_2, A_4 and A_6 bears an aromatic side chain, which aromatic side chains are cross-linked together by two or more covalent bonds, and (iii) the group A_7 bears a terminal carboxyl, ester, thioester, amide, N-substituted amide, or other derivative of a carboxylic acid.

In the compounds of the present invention, one or more of the groups A_2 to A_7 is linked via a glycosidic bond to one or more sugar resides; wherein at least one of said sugar resides bears at least one hydrophobic substituent wherein the hydrophobic substituent is preferably

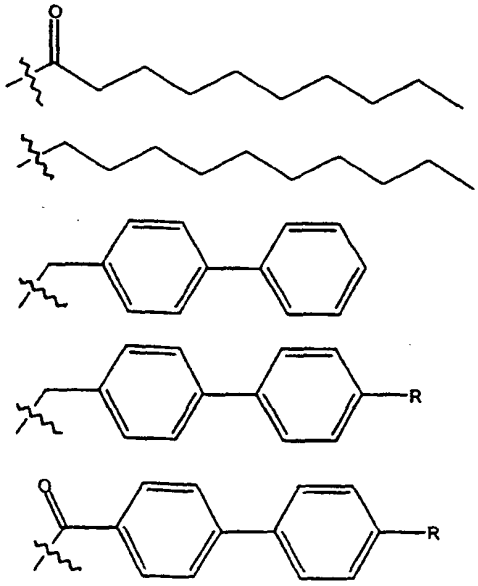
selected from R, OR, NR_1R, SR, SO_2R, C(O)OR, C(O)SR, C(S)OR, C(S)SR, $NR_1C(O)R$, $C(O)NR_1R$, or halo and R is alkyl, aryl, aralkyl, alkanoyl, aroyl, aralkanoyl, heterocyclic, heterocyclic-carbonyl, heterocyclic-alkyl, heterocyclic-alkyl-carbonyl, alkylsulfonyl or arylsulfonyl; R_1 is hydrogen, alkyl, aryl, aralkyl, alkanoyl, aroyl, aralkanoyl, heterocyclic, heterocyclic-carbonyl, heterocyclic-alkyl, heterocyclic-alkyl-carbonyl, alkylsulfonyl or arylsulfonyl; and any pharmaceutically acceptable salts thereof; and if two or more of said substituents are present, they can be the same or different.

Modified amino acid residues include amino acid residues whose aromatic groups have been substituted by halo, alkyl, alkoxy, alkanoyl, or other groups easily introduced by electrophilic substitution reactions or by reaction of phenolic hydroxyl groups with alkylating or acylating agents; and amino acid residues which have protecting groups or other easily introduced substituents on their hydroxyl or amino groups including, but not limited to alkyl, alkanoyl, aroyl, aralkyl, aralkanoyl, carbamoyl, allyloxycarbonyl, aralkyloxycarbonyl, aryloxycarbonyl, alkylsulfonyl, arylsulfonyl, heterocyclic, heterocyclic-alkyl or heterocyclic-carbonyl substituents. Examples of preferred protecting groups include acetyl, allyloxycarbonyl (aloc), CBZ, allyl, benzyl, p-methoxybenzyl and methyl. Modifications of hydroxyl groups occur on phenolic hydroxyl groups, benzylic hydroxyl groups, or aliphatic hydroxyl groups. Other amino acid residues, in addition to A_2, A_4 and A_6 may be cross-linked through their aromatic acid substituent groups.

In the preferred compounds of the present invention, the residues A_2 to A_7 of the glycopeptides are linked sequentially by peptide bonds and are cross-linked as in a dalbaheptide. The preferred glycopeptides have a peptide core in which the residues are linked as in the glycopeptide antibiotics vancomycin, eremomycin, chloroeremomycin or β-avoparcin. In

particularly preferred compounds of the present invention, the structures and interconnections of A_2 to A_7 are those of vancomycin, i.e., those having the heptapeptide core of vancomycin with the N-methyl leucine residue removed, subject to the amino acid modifications and substitutions described herein above.

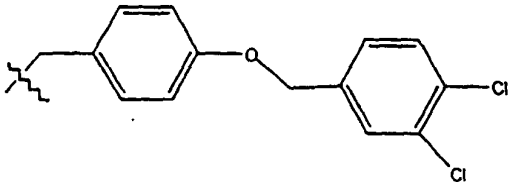
The glycopeptide compounds of the present invention contain at least one glycosidic group attached through a glycosidic bond to at least one of the amino acid residues A_2 to A_7. In the preferred compounds of the present invention, a glycosidic group is linked to residue A_4. This glycosidic group comprises at least a monosaccharide bearing at least one hydrophobic substituent. Preferably, the glycosidic group is a disaccharide residue bearing at least one hydrophobic substituent which disaccharide residue can be linked to any of the amino acid residues A_2-A_7, preferably to the amino acid residue A_4. In the particularly preferred compounds of the present invention, the glycosidic group attached to A_4 is a disaccharide consisting of a glucose residue directly attached to the amino acid A_4 and an N-substituted vancosamine residue attached to the glucose residue. Preferably, the vancosamine residue is N-substituted with the at least one hydrophobic substituent. Examples of preferred hydrophobic substituents which are preferably present as N-substituents on the vancosamine residues are shown below:

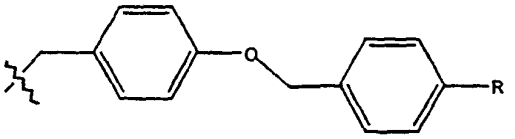


Chain lengths from C_8 to C_{15} could also be branched alkyl, halo alkyl, halo alkoxy.

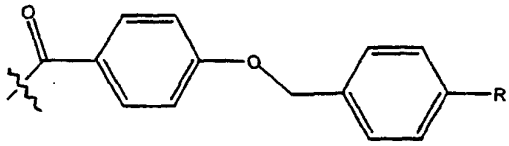
R= Halogen, C_4 to C_8 alkyl, C_4 to C_8 alkoxy, could also have more R groups (up to five)

R= Halogen, C_4 to C_8 alkyl, C_4 to C_8 alkoxy, could also have more R groups (up to five)

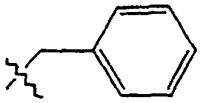


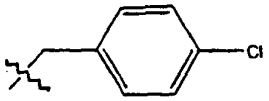


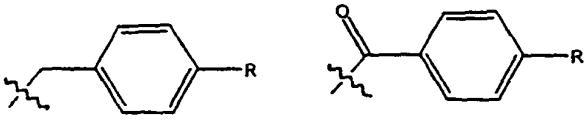
R= Halogen, C_4 to C_8 alkyl, C_4 to C_8 alkoxy, could also have more R groups (up to five)



R= Halogen, C_4 to C_8 alkyl, C_4 to C_8 alkoxy, could also have more R groups (up to five)







R= Halogen, O-Butyl, O-Octyl, Butyl, Octyl could also have more than one R group

Thus, preferred N-substituents at the vancosamine nitrogen include, e.g., straight or branched alkyl, aralkyl, alkanoyl, aralkanoyl and aroyl. Any of these N-substituents may be substituted with one or more of alkyl, preferably C_4-C_8 alkyl, halo, haloalkyl, aryl, aralkyl, aryloxy, aralkyloxy, alkaryloxy, alkoxy, preferably C_4-C_8 alkoxy, and haloalkoxy. Preferred alkoxy substituents on the N-substituent include, e.g., O-butyl and O-octyl. Where the N-substituent is alkyl, it is preferred that alkyl has from 8 to 15 carbon atoms. Specific preferred N-subsitutents include, but are not limited to the following:

2-naphthylmethyl
4-phenylbenzyl
1-naphthylmethyl
4-phenoxybenzyl;
4-benzyloxybenzyl
4-trifluoromethoxybenzyl
4-allyloxybenzyl
4-nonyloxybenzyl;
2-methoxy-1-naphthylmethyl
4-dodecyloxybenzyl
9-phenanthranylmethyl
4-decyloxybenzyl
9-anthranylmethyl
4-[phenylethynyl]4-phenylbenzyl
4-methoxy-1-naphthylmethyl
1-pyrenylmethyl
9-[10-methyl]anthranylmethyl
9-[10-chloro]anthranylmethyl
2-benzthienylmethyl
4-[4-hydroxyphenyl]benzyl
4-[4-octylphenyl]benzyl
4-[4-pentylphenyl]benzyl
4-[4-octyloxyphenyl]benzyl
3-pyridylmethyl
5-nitro-1-naphthylmethyl
4-pyridylmethyl
4-quinolylmethyl
3-quinolylmethyl
4-stilbenzyl
2-quinolylmethyl
2-pyridylmethyl
2-fluorenylmethyl
4-phenoxyphenethyl
4-[4-pentylcyclohexyl]benzyl
4 -benzylphenethyl
4-[4-biphenyl]benzyl
4-trifluoromethylbenzyl
trans-cinnamyl
4-[1-oxa]fluorenylmethyl
4-[4-pentoxyphenyl]benzyl
4-thiomethylbenzyl
2,3-[2-methyl-3-›4-t-butylphenyl]]propenyl
9-(1-methyl)-acridinylmethyl
2-hydroxy-1-naphthylmethyl

4-[2-phenyl-6-methoxy]quinoylmethyl
4-diphenylmethylbenzyl
3,4 cyclohexenylmethyl
3,4-methylenedioxylbenzyl
3-phenoxybenzyl
4-benzylbenzyl
3-benzyloxy-6-methoxy benzyl
4-benzyloxy-3-methoxybenzyl
3,4-dibenzyloxybenzyl
4-[4-methoxyphenyl]benzyl
4-[3-cyanopropoxy]benzyl
3,4-ethylenedioxybenzyl
4-[4-nitrophenoxy]benzyl
2,3-methylenedioxybenzyl
2-benzyloxyphenethyl
2-ethoxy-1-naphthylmethyl
2-benzylfurylmethyl
3-phenoxyphenethyl
4-phenoxyphenethyl
4-[4-nitrophenyl]benzyl
6-methoxy-2-naphthylmethyl
3-methyl-5-thienylmethyl
5-phenyl-2-thienylmethyl
4-benzyloxyphenethyl
3-benzyloxyphenethyl
4-[2-nitrophenoxy]benzyl
5-[4-methoxyphenyl]-2-thienylinethyl
4-difluormethoxybenzyl
2,3,4,5,6-pentamethylbenzyl
5-iodo-2-thienylmethyl
4-[2-[2-chloroethoxy]ethoxy]benzyl
3,4-dimethylbenzyl
3-acetoxybenzyl
4-nitrobenzyl
4-phenylethynylbenzyl
4-[2-chloro-6-fluorobenzyloxy]benzyl
4-[3,4-dichlorophenoxy]benzyl
4-[3,4-dichlorobenzyloxy]benzyl
S-[2,3-dihydrobenzfuryl]methyl
4-[2-[N,N-diethylamino]ethoxy]benzyl
2-bicyclo[2.1.2]heptylmethyl
2-hydroxy-5-phenylbenzyl
3-[4-chlorophenoxy]benzyl
4-[3-chlorophenoxy]-3-nitrobenzyl
4-[2-chlorophenoxy]-3-nitrobenzyl

3,5-dimethylbenzyl
4-[4-ethylphenyl]benzyl
3-phenylbenzyl
4-[3-fluorophenyl]benzyl
4-[4-chlorobenzyloxy]benzyl
4-[4-chlorophenoxy]-3-nitrobenzyl
4-[4-methylphenoxy]benzyl
4-[4-t-butylphenoxy]benzyl
4-[4-methylphenyl]benzyl
4-[4-methoxyphenoxy]benzyl
4-acetoxy-3-methoxybenzyl
4-[(2-phenyl)ethyl]benzyl
3-[5-phenyl]pyridinylmethyl
4-[2-nitrophenyl]benzyl
2-[1-hydroxy]fluorenylmethyl
4-benzyl-3-methoxybenzyl
4-[cyclohexylmethoxy]-3-ethoxybenzyl
3-[3,3'-dichlorophenoxy]benzyl
4-[4-propylphenyl]benzyl
4-thiophenylbenzyl
4-[alpha-hydroxybenzyl]benzyl
2,2-dinitro-4-thiophenebenzyl
3-[3-trifluoromethylphenoxy]benzyl
4-[t-butylethynyl]benzyl
4-phenoxy-3-methoxy-benzyl
4-[3-trifluoromethylphenoxy]-3-nitrobenzyl
2-phenylthiobenzyl
2-[4-chlorophenyl]-6-benzoxazolemethyl
4-[alpha-methoxybenzyl]benzyl
4-cyclohexylbenzyl
3-[3,4-dichlorophenoxy]benzyl
acenaphthlenylmethyl
4-[1,1,2,2-tetrafluoroethoxy]benzyl
4-benzoyloxy-3,3-dimethoxybenzyl
3-[cyclohexylmethoxy]benzyl
4-cyclohexyloxybenzyl
3-[2-quinoylmethoxy]benzyl
4-[alpha-ethoxybenzyl]benzyl
4-[cyclohexylethoxy]benzyl
4-[alpha-propoxybenzyl]benzyl
4-[4-methyl-1-piperidino]benzyl
2-thiophene-1,2-cyclohexenylmethyl
4-[4-nitrobenzyloxy]benzyl
3-[4-trifluoromethylphenoxy]benzyl
3-benzoyl-2,4-dichlorobenzyl

4-[2-[2-thiopropyl]ethoxy]benzyl
4-[2-methyl-1-piperidino]benzyl
4-hydroxybenzyl
4-[2-pyridyl]benzyl
4-acetoxybenzyl
5,6-benzonorbornylmethyl
3-phenylcyclopentylmethyl
1-adamantylmethyl
3-[cyclohexylmethoxy]-4-methoxybenzyl
2-[2-glucosyl]benzyl
4-[4-pentoxybiphenyl]benzyl
3,4-dihydroxybenzyl
4-[4-methylpiperazino]benzyl
4-morpholinobenzyl
4-[4-chlorophenylsulfonyl]benzyl
4-methylsulfonyloxybenzyl
4-benzoyloxybenzyl
5-phenyl-3-pyridinylmethyl
4-[N,N-bis(2-chloroethyl)amino]benzyl
3-cyclohexyloxybenzyl
4-[2-t-butoxyethoxy]benzyl
3,3-dichloro-4-hydroxy-benzyl
1,2,3,4,-tetrahydro-9-anthranylmethyl
4-cyclohexanoyloxybenzyl
4-nonanoyloxybenzyl
4-[phenylsulfinyl]benzyl
4-anilinobenzyl
cyclohexylmethyl
3-benzoyloxybenzyl
3-nonanoyloxybenzyl
4-[cyclohexyl]cyclohexylmethyl
3-cyclohexanoyloxybenzyl
4-[cyclohexanoyloxy]-3,3-›dimethoxy]benzyl
4-[nonanoyloxy]-3,3-›dimethoxy]benzyl
1,2,3,4-tetrahydro-6-naphthylmethyl
2-hydroxybenzyl
[2-[6,6-dimethyl-bicyclo›3.1.1]hept-2-enyl]methyl
1-cyclohexenyl-4-isopropylmethyl
4-[4-methoxyphenyl]butyl
4-[[2,3,4,5,6-pentamethyl]phenylsulfonyloxy]benzyl
4-[1-pyrrolidinosulfonyl]benzyl
3-[4-methoxyphenyl]propyl
8-phenyloctyl
4-[2,3-dihydroxypropoxy]benzyl
4-[N-methylanilino]benzyl

2-[2-napthyl]ethyl
6-methyl-2-naphthylmethyl
cis-bicyclo[3.3.0]octane-2-methyl
2-tridecynyl
4-butyl-2-cyclohexylmethyl
4-[(4-fluorobenzoyl)amino]benzyl
4-[(3-fluorobenzoyl)amino]benzyl
8-phenoxyoctyl
6-phenylhexyl
10-phenyldecyl
8-bromooctyl
11-tridecynyl
8-[4-methoxyphenoxy]octyl
8-[4-phenylphenoxy]octyl
8-[4-phenoxyphenoxy]octyl
3-[3-trifluoromethylphenoxy]benzyl
10-undecenyl
4-cyclohexylbutyl
4-phenyl-2-fluorobenzyl
7-hexadecynyl
3-[cyclopentyl]propyl
4-[2-methylphenyl]benzyl
4-[phenylazo]benzyl
4-[4-flurophenyl]benzyl
3-nitro-4-[4-nitrophenyl]benzyl
3-nitro-4-[2-nitrophenyl]benzyl
9-decenyl
4-[3,4-dimethoxyphenyl]benzyl
4-[4-trifluromethylphenyl]benzyl
5-hexenyl
4-[2-thienyl]benzyl
4-[6-phenylhexyloxy]benzyl
9,10-dihydro-2-phenantrene methyl
4-[3,4-dimethylphenyl]benzyl
4-[4-methylphenyl]-2-methylbenzyl
4-[3-phenylpropyloxy]benzyl
4-[3-methylphenyl]benzyl
4-[4-methylphenyl]-3-methylbenzyl
4-[4-pentenyloxy]benzyl
4-[1-heptynyl]benzyl
3-[4-t-butyl-phenylthio]benzyl
4-[4-chlorophenyl]benzyl
4-[4-bromophenyl]benzyl
4-[4-cyanophenyl]benzyl
4-[1-nonynyl]benzyl

4-[11-tridecynyloxy]benzyl
12-phenyldodecyl
6-phenyl-5-hexynyl
11-phenyl-10-undecynyl
4-[2-methylphenyl]-3-methylbenzyl
3-[2-thienyl]-2-thienylmethyl
4-[benzyloxymethyl]cyclohexylmethyl
4-[4-chlorophenoxy]benzyl
4-[benzyl]cyclohexylmethyl
4-benzoylbenzyl
4-[phenoxymethyl]benzyl
4-[4-chlorobenzyl]benzyl

In another preferred embodiment of the present invention, the glucose residue attached to A_4 is modified to bear a substituent, which may be any of the hydrophobic substituents as described above as well as polar substituents. Thus, the preferred compounds of the present invention encompass compounds in which the vancosamine residue is N-substituted with a hydrophobic substituent and the glucose residue is modified to bear a substituent other than hydroxyl. Preferably, it is the C_6 position of the glucose residue that is modified to bear a substituent other than hydroxyl as described above. Thus, in particularly preferred compounds of the present invention, the vancosamine residue is N-substituted with a hydrophobic substituent and the glucose residue is also modified at the C_6 position to bear a substituent other than hydroxyl. Where the vancosamine residue is N-substituted with a hydrophobic substituent and the glucose residue is also modified to bear a substituent other than hydroxyl, it is preferred that glucose residue attached to A_4 is substituted with a polar substituent. Examples of preferred substituents on the glucose residue, and in particular at the C_6 position of the glucose residue include, but are not limited to, mesitylenesulfonyl; 2-thio-6-azathymine; 2-thio-4-hydroxy-6-methylpyrimidine; 2-thio-5-amino-1,3,4-thiadiazole; 2-thio-4-amino-3-hydrazino-1,2,4-triazole; 2-thio-4-hydroxy-6-methylpyrimidine; 2-thio-6-azathymine; iodo; amino; azido; bromo;

hydrazino; iminotriphenylphosphoranyl; S-3-amino-5-mercapto-1,2,4-triazolyl; N-2-quinoxalinyl-Vancosamine. It is to be understood that the C_6 position can also be modified to bear any of the hydrophobic substituents as described above. Thus, where the C_6 position of the glucose residue attached directly to A_4 is modified to bear a hydrophobic substituent as described above, it is not necessary that the vancosamine residue attached to the glucose residue also bear a hydrophobic substituent as well. However, it is possible that both the glucose and vancosamine glycosidic groups at the A_4 position can be modified to bear a hydrophobic substituent.

The invention is not intended to be limited to the embodiments described above. Thus, beneficial effects of at least some of the A_1 substituent replacements on a dalbaheptide in which A_1 is not covalently linked to A_3 would be expected to apply generally to glycopeptide derivatives containing at least one hydrophobic group on a sugar covalently bonded to the peptide.

The compounds of the present invention can be prepared by removing the terminal N-substituted leucine residue from a compound of the formula N-substituted leucyl-A_2-A_3-A_4-A_5-A_6-A_7 wherein at least one of the glycosidic groups attached to any of A_2-A_7 bears a hydrophobic substituent to form the compound des-N-substituted-leucyl-A_2-A_3-A_4-A_5-A_6-A_7 bearing a free amino group at A_2 and then attaching the group A_1 to the free amino group at A_2 to form a compound of the present invention. The N-substituted leucine residue is preferably N-methyl leucine. The terminal N-substituted leucine residue can be removed by any conventional process for removing a terminal amino acid from an oligopeptide or polypeptide. One conventional method to remove a terminal amino acid is Edman degradation. This method is described in the literature and can be readily employed to remove a terminal N-substituted leucine residue in a

process of making the compounds of the present invention. As applied to the method of forming the des-N-methyl leucyl compounds of the present invention, Edman degradation involves the reaction of the amino group of the terminal N-methyl leucine residue with phenyl isothiocyanate in a suitable solvent. An intermediate thiourea compound is formed, and the N-methyl leucine residue splits off from the thiourea as a phenylthiohydantoin, resulting in the corresponding des-N-methyl leucine compound.

Thus, the N-methyl leucine residue can be removed from the compound N-methyl leucyl-A_2-A_3-A_4-A_5-A_6-A_7 by reacting this compound with phenylisothiocyanate in a suitable organic solvent, preferably a pyridine-water solvent, more preferably, a 1:1 pyridine-water solvent at a temperature of about 50 °C. This reaction generates the corresponding thiourea, which is then treated with TFA-CH_2Cl_2 to yield the des-N-methyl leucyl compound, to which the group A_1 can optionally be attached as described in more detail below.

The present inventors have also discovered a modified Edman degradation procedure by which an N-terminal amino acid residue can be removed from a polypeptide or an oligopeptide. This procedure involves reacting the N-terminal amino acid residue on the polypeptide or oligopeptide with phenylisothiocyanate in a pyridine-water-triethylamine solvent medium. The pyridine-water-triethylamine solvent medium preferably comprises pyridine-water-triethylamine in a ratio of 10:10:1 by volume. The reaction is conducted for about 20 to 60 minutes, with 60 minutes preferred. While not wishing to be bound by any particular theory, it is believed that triethylamine is a key reagent in this modified Edman degradation protocol. It is believed that the triethylamine catalyzes the *in situ* conversion of the initially formed thiourea to the final product.

In the context of the present invention, the modified Edman degradation process

described above can be applied to remove the terminal N-substituted leucine residue from the compound N-substituted leucyl-A_2-A_3-A_4-A_5-A_6-A_7 wherein at least one glycosidic group attached to any of A_2-A_7 bears a hydrophobic substituent to yield the corresponding desleucyl compound bearing a free amino group at A_2 which can then be reacted with the organic group A_1 to yield the compounds of the present invention. Thus, the compound N-substituted leucyl-A_2-A_3-A_4-A_5-A_6-A_7, wherein the N-substituted leucine residue is preferably N-methyl leucine, is reacted with phenylisothiocyanate in a pyridine-water-triethylamine solvent medium, preferably a 10:10:1 pyridine-water-triethylamine solvent medium and at a temperature of about 50 °C. This method yields the corresponding des-N-methyl leucyl compound in one step in nearly quantitative yield. The desired des-N-methyl leucine compound can be precipitated from DMF by adding excess of 20% ethyl acetate-hexane. The resulting product is then suitably pure for a subsequent optional step of attaching the group A_1 to the free amino group at A_2 on the des-N-methyl leucine compound to form a compound of the present invention.

Any conventional method can be employed to attach the group A_1 to the free amino group at A_2 after removal of the terminal N-substituted leucine residue. Such methods of coupling amino groups to other organic groups are well known to the ordinarily skilled chemist. In the preferred compounds of the present invention the group A_1 is attached to the free amino group at A_2 by forming an amide linkage. Thus, a carboxylic acid or other amine- reactive compound can be reacted with the free amino group at A_2 to form preferred compounds of the present invention. It is also possible to attach the organic group to the free amino group at A_2 by reductive alkylation or other common methods of functionalizing amino groups. It may be desirable in some cases when attaching the group A_1 to the free amino group at A_2 to suitably protect free amino groups at other positions in the intermediate compound so as to selectively attach the A_1

group to the free amino group at A_2. Such methods of selectively protecting free amino groups and selectively removing the protective groups are well known to the ordinarily skilled chemist. Suitable protecting groups for free amino groups include 9-fluorenylmethyloxycarbonyl (Fmoc), benzyloxycarbonyl (CBZ), tert-butyloxycarbonyl (t-Boc), and allyloxycarbonyl (alloc).

Preferably, the terminal N-substituted leucine residue is removed from a dalbaheptide wherein at least one of the groups A_2-A_7 is linked via a glycosidic bond to one or more glycosidic groups each having one or more sugar residues and wherein at least one of the sugar residues is modified to bear at least one hydrophobic substituent as described above. Thus, for example, N-methyl leucine can be removed from the dalbaheptide vancomycin in which the vancosamine residue is N-substituted with a hydrophobic substituent and which optionally may also be substituted on the glucose residue, preferably at the C_6 position thereof, with either a hydrophobic or, more preferably, a polar substituent as described above. Also, N-methyl leucine can be removed from the dalbaheptide vancomycin in which the C_6 position is modified to bear a hydrophobic substituent and in which the vancosamine nitrogen optionally also bears a hydrophobic substituent. The modified des-N methyl leucyl vancomycin can then be reacted to attach the A_1 substituent to form the compounds of the present invention.

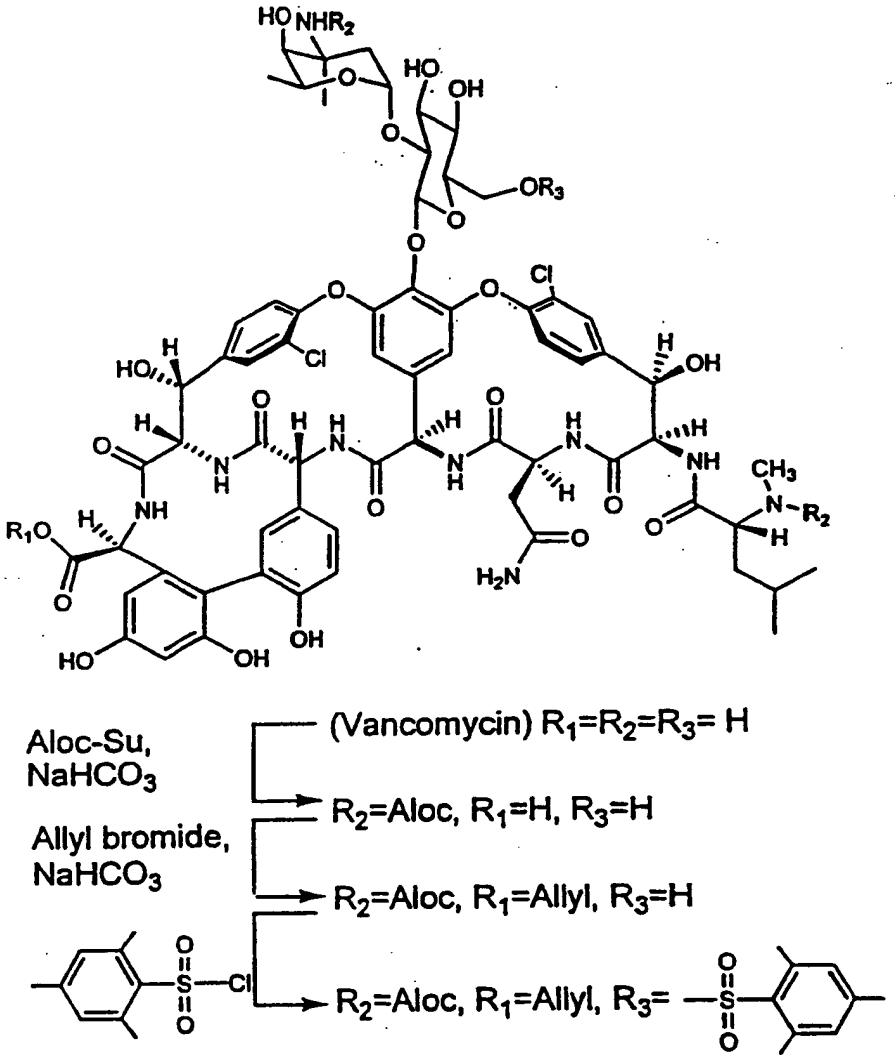
An N-substituted vancomycin glycopeptide can be prepared by attaching a hydrophobic substituent to the amino group on the vancosamine residue by reductive alkylation or other conventional methods for functionalizing an amino group. Thus for example, an aldehyde can be reacted with vancomycin in a suitable organic solvent, followed by reduction of the aldehyde carbonyl group with a suitable reducing agent followed by conventional separation and purification, which may involve recrystallization and/or reverse phase chromatographic techniques as are well known to the ordinarily skilled chemist. In some cases it may be desirable

to selectively protect the amino group in the N-methyl leucine residue prior to the reductive alkylation of the vancosamine nitrogen. Any amino protecting group may be employed and conventional methods of removing the amino protecting group may be employed to remove the protective group after performing the reductive alkylation at the vancosamine nitrogen. Other methods of coupling free amino groups to organic substituents can also be employed to attach the hydrophobic substituent the vancosamine amino group. Thus, reductive alkylation is merely a preferred method of attaching the hydrophobic group to this position of the vancosamine residue, and other methods will be apparent to the person having ordinary skill in the art.

As discussed above, in addition to modifying a glycosidic group to bear at least one hydrophobic substituent as described above in connection with the vancosamine nitrogen, it may also be desirable to modify another glycosidic group to bear a hydrophobic or polar substituent. In fact, any glycosidic group attached to any of the amino acid residues A_2-A_7 can be modified to bear a hydrophobic substituent in accordance with the present invention. Thus, any of the glycosidic groups in, e.g., the glycopeptide antibiotics vancomycin, eremomycin, chloroeremomycin, and β-avoparcin can be modified to bear at least one hydrophobic substituent. Thus, the present invention is not to be construed as limited to the preferred compounds which comprise a hydrophobic substituent at the vancosamine nitrogen and, optionally, a substituent at the C_6 position of the glucose residue directly attached to amino acid A_4 in vancomycin.

It is to be understood that where vancomycin is modified to bear a substituent at the C_6 position of the glucose residue directly attached to A_4, this substituent may be hydrophobic or polar, however, it is preferred that where the vancosamine nitrogen position is modified to bear a hydrophobic substituent, the C_6 position, when modified, will preferably be modified to bear a

polar substituent. Where the C_6 position of glucose attached to A_4 of vancomycin is to be modified to bear a substituent, the following strategy may be employed to introduce a suitable set of protecting groups onto vancomycin and to differentiate the C_6 hydroxyl group of the glucose residue on A_4 of vancomycin from all other hydroxyl groups. This strategy may be generally employed to modify any selected hydroxyl group of a glycopeptide antibiotic which need not be limited to vancomycin, although C_6 modification of the glucose residue attached to A_4 of vancomycin is preferred. Thus, the following method is particularly suitable for modification of, e.g., a primary hydroxyl group on any glycosidic group attached to any of the amino acid residues A_2-A_7. Thus, while the foregoing method is described in reference to the primary hydroxyl group at the C_6 position of the glucose residue directly attached to A_4 of vancomycin, it is to be understood that the synthetic method described below is applicable to any similarly reactive hydroxyl group on any glycosidic group attached to any of the amino acid residues A_2-A_7. A schematic which generally illustrates the modification of the C_6 position of vancomycin is shown below:


Aloc-Su,
NaHCO3
(Vancomycin) R1=R2=R3= H
R2=Aloc, R1=H, R3=H
Allyl bromide,
NaHCO3
R2=Aloc, R1=Allyl, R3=H
R2=Aloc, R1=Allyl, R3=

Protection of both amines by similar groups requires using excess acylation reagent while selective protection of the N-methyl leucine residue is known, allowing selective functionalization of the vancosamine amine group. See Pavlov et al., J. Antibiotics, 1993, 46, 1731, incorporated herein in its entirety. Selectively introducing the mesitylenesulfonyl group at the glucose C_6 position differentiates this position from the other hydroxyl groups and allows further reaction to displace the mesitylenesulfonyl group, affording may derivatives. A variety of functional groups are introduced at the glucose C_6 position by using common methods for nucleophilic displacement of primary arylsulfonyl groups directly, or by further synthetic modification of initial displacement products, including azido and iodo groups. For example, the iodo group is displaced by a variety of nucleophiles to produce additional C_6 derivatives. A preferred nucleophile is a thiol compound, especially a heterocyclic thiol. Modification of an azido group at the C_6 position is performed, e.g., by reducing the azido group to an amino group, which in turn is functionalized by means of reductive alkylation, nucleophilic substitution, or other amino-group reactions well known to those skilled in the art. In a preferred embodiment of the invention, an azido group is partially reduced by reaction with a phosphine compound to produce an iminophosphorane. In a preferred method of modifying the C_6 position, or other similarly reactive hydroxyl group on a glycosidic group, the C_6 position is modified to bear a free amino group by displacing the mesitylenesulfonyl group with an azido group which is then reduced to the free amino group. The free amino group at the C_6 position can then be further modified to bear, e.g., a hydrophobic substituent by reacting the free amino group in a manner similar to that described above with respect to attaching a hydrophobic substituent to the vancosamine nitrogen.

In the process described above, the vancosamine amino group, the N-methyl leucine

amino group and the carboxyl group at A_7 of vancomycin are suitably protected. Then, the C_6 hydroxyl is substituted with a mesitylenesulfonyl group which, as described above can be further displaced, e.g., by nucleophilic displacement to afford many derivatives. While the above method has been described in connection with attachment of mesitylenesulfonyl group at the C_6 position, it is to be understood that after suitably protecting the glycopeptide starting compound, the C_6 hydroxyl group can be reacted with any compound that will attach a good leaving group to the C_6 position. The leaving group may then be displaced by a subsequent reaction, e.g., by nucleophilic displacement, and further derivatization may then be performed at the C_6 position yielding many derivatives. The groups protecting the vancosamine amino group, the N-methyl leucine amino group and the carboxyl group at A_7 can be removed in a conventional manner.

Where the C_6-substituted vancomycin analog is to be further substituted with a hydrophobic substituent at the vancosamine nitrogen, the protecting groups at the vancosamine amino group, at the carboxyl group at A_7 and at the N-methyl lecuine amino group of the C_6-substituted vancomycin are removed. The vancosamine nitrogen is then substituted with the hydrophobic substituent in the manner described above, e.g., by performing a reductive alkylation reaction. The N-methyl leucine residue is removed from this compound and the group A_1 is attached to the free amino group at A_2 as described above. The resulting compound, may then be further modified at the C_6 position as described above in connection with the C_6 derivatization, thus affording many derivatives. The resultant product, after separation and purification will thus have a hydrophobic substituent at the vancosamine nitrogen position and will have been modified to bear a group other than hydroxyl at the C_6 position of the glucose residue, and will also have an organic group other than N-methyl leucine attached to the amino acid A_2.

Preferably, the N-substituted leucine residue is removed from a compound in which one or more of the glycosidic groups attached to one of the amino acid residues A_2-A_7 is already modified to bear the at least one hydrophobic substituent. However, it is also possible to modify the glycosidic group either prior to or after removal of the N-substituted leucine residue. Thus, it is possible to attach one or more glycosidic groups onto a glycopeptide antibiotic, pseudoaglycone or aglycone bearing a terminal N-substituted leucine residue and then modifying the glycosidic group to bear the at least one hydrophobic substituent. Furthermore, the modification of the glycosidic group can also be conducted either prior to or after attachment of the A_1 group upon removal of the terminal N-substituted leucine residue.

The glycosidic group can be attached to any reactive hydroxyl group in a glycopeptide antibiotic, aglycone or pseudoaglycone. Preferably the glycosidic group is attached to an aglycone or to a pseudoaglycone. Where the glycosidic group is attached to an aglycone, it is preferable to attach a second glycosidic group to the previously attached glycosidic group, which results in a disaccharide group attached to one of the amino acid residues in the aglycone. Preferably, the sequential attachment of glycosidic groups is performed at the A_4 position of an aglycone, however, it is to be understood that this method can be generally applied to any of the amino acid residues forming an aglycone, pseudoaglycone or glycopeptide antibiotic. The glycosidic groups can be attached to any of the reactive hydroxyl groups in glycopeptide antibiotics, aglycones or pseudoaglycones. These reactive hydroxyl groups are generally phenolic hydroxyl groups, benzylic hydroxyl groups or aliphatic hydroxyl groups. Thus, a glycosidic group can be introduced at any of such hydroxyl groups as desired. Moreover, as discussed above, a glycosidic group can also be attached to a previously attached glycosidic group, which results in a disaccharide group attached to one of the amino acid residues in the

aglycone, pseudoaglycone or glycopeptide antibiotic. Any hydroxyl group on the glycopeptide antibiotic, aglycone or pseudoaglycone to which a glycosidic group is not desired to be attached can be suitably protected. Also, the glycosidic group itself may be suitably protected so that the desired glycosidic bond to the glycopeptide antibiotic, aglycone or pseudoaglycone is formed.

Thus, a glycopeptide antibiotic having a terminal N-substituted leucine residue can be prepared by (a) selecting: (i) an aglycone that is soluble in one or more organic solvents, is derived from a glycopeptide antibiotic, and which aglycone has exactly one free phenolic hydroxyl group; and (ii) a protected first glycosyl donor; (b) allowing a non-enzymatic glycosylation reaction to proceed in an organic solvent such that a first glycosidic bond is formed, which links said free phenolic hydroxyl group to the anomeric carbon of the first glycosyl donor to provide a pseudoaglycone having a protected first glycosyl residue; (c) selectively removing one protecting group from the first glycosyl residue to provide a pseudoaglycone bearing exactly one free hydroxyl group on the first glycosyl residue; (d) selecting a second protected glycosyl donor; and (e) allowing a non-enzymatic glycosylation reaction to proceed in an organic solvent such that a second glycosidic bond is formed which links said free hydroxyl group on the pseudoaglycone to the anomeric carbon of the second glycosyl donor. Any of the glycosidic groups on the resultant compound can be modified to bear the at least one hydrophobic substituent in accordance with the preferred methods as described above. Any glycosidic group can be attached to an aglycone, pseudoaglycone or glycopeptide antibiotic in the foregoing manner. Thus, it may be desirable to attach a glycosidic group bearing a free amino group to an aglycone, pseudoaglycone or glycopeptide antibiotic as described above. A hydrophobic substituent can then be attached to the free amino group to produce a compound having a glycosidic group bearing at least one hydrophobic substituent in accordance with the

present invention. Attachment of a glycosidic group with a free amino group is advantageous because it may avoid the necessity of functionalizing the glycosidic group to bear an amino group prior to attaching the hydrophobic substituent thereto.

It is apparent that the method described above can be modified by starting with a pseudoaglycone and then attaching another glycosidic group thereto. Thus it is to be understood that the method of suitably protecting and deprotecting hydroxyl groups can be generally applied to selectively attach a glycosidic group to any desired hydroxyl group on an aglycone, pseudoaglycone or glycopeptide antibiotic, any of which may be modified to bear a hydrophobic substituent on a glycosidic group.

Where it is desired to attach glycosidic groups to an aglycone, pseudoaglycone or glycopeptide antibiotic, all reactive functional groups on any of these starting compounds are suitably protected. Thus, amine, carboxylic acid, phenolic and benzylic hydroxyl groups, e.g., need to be protected to avoid their participation in the reaction that attaches the glycosidic group. The protecting groups are suitably chosen so as to render the protected compounds soluble in the reaction medium. The protecting groups may remain on the final compound, but are preferably removed by exposure to acidic or basic conditions, catalytic hydrogenation, or light or other conventional methods for removing protecting groups. Any conventional protecting groups for the functional groups mentioned above may be employed. When the aglycone, pseudoaglycone or glycopeptide antibiotic is or is derived from vancomycin, it is preferred that the protecting groups are as follows: carboxybenzyl (CBz) on the amino nitrogen, a benzyl ester group; benzyl, allyl or methyl phenolic ethers on the phenolic hydroxyls of A_5 and A_7, and acetates on the aliphatic hydroxyls. Removal of the protective groups can be accomplished by methods well known to the ordinarily skilled organic chemist. Thus, when it is desired to remove protecting

groups from any of the compounds of this invention, their removal is accomplished using methods well known to those skilled in the art. The preferred method for removal of protecting groups is as follows. Aloc groups on amines, and allyl esters or allyl ethers are removed by using Pd(0) mediated reactions, e.g., $[Ph_3P]_2Pd(II)Cl_2$ and Bu_3SnH in 1:1 acetic acid:DMF. Acetate protecting groups are removed using hydrazine in THF/methanol. The use of protecting groups to protect any group which might otherwise be reactive under a particular set of reaction conditions is well known to the ordinarily skilled artisan. As will be apparent to the ordinarily skilled artisant, any such conventional protecting groups and the methodologies employed therewith can be used in the present invention.

The suitably protected aglycone, pseudoaglycone or glycopeptide antibiotic is glycosylated via a non-enzymatic reaction in an organic solvent with a variety of glycosyl donors, thereby forming a glycosidic bond between the aglycone, pseudoaglycone, glycopeptide antibiotic and the glycosyl donor. Preferably, the glycosyl donors are activated monosaccharide anomeric sulfoxides which are fuctionalized at the 6 position or elsewhere. These sulfoxide donors are differentially protected so as to allow for selective deprotection of a single hydroxyl after formation of the glycosidic bond. The single hydroxyl can then be the reactive site for forming another glycosidic bond with a glycosidic group. Suitable protecting groups to allow for this selective deprotection include, but are not limited to, the 2,2-dimethyl acetoacetate group, the 4-azidobutyryl group and any other groups which can be removed in the presence of other protecting groups.

Glycosidic groups can also be removed from a glycopeptide antibiotic or pseudoaglycone. Thus, a glycosidic group can be removed from a glycopeptide antibiotic by (a) selecting a glycopeptide antibiotic that is soluble in one or more organic solvents; (b) contacting the

glycopeptide antibiotic with a Lewis acid, and allowing a degradation reaction to proceed such that a sugar residue is removed, producing a pseudoaglycone having exactly one free hydroxyl group on a remaining sugar residue of the pseudoaglycone; a glycosidic group can then optionally be attached to the free hydroxyl group on the pseudoaglycone by the subsequent steps of (c) selecting a protected glycosyl donor; and (d) allowing a non-enzymatic glycosylation reaction to proceed in an organic solvent such that a glycosidic bond is formed which links the free hydroxyl group of the remaining sugar residue on the pseudoaglycone to the anomeric carbon of the glycosyl donor. Thus, the foregoing method can be applied to removal of a glycosidic group, e.g., from a glycopeptide antibiotic having a disaccharide attached to A_4. The glycopeptide antibiotic bearing a disaccharide at A_4 is treated with a Lewis acid in an organic solvent to remove a sugar residue from the disaccharide group. The Lewis acid is preferably boron trifluoride, preferably as a complex with diethyl ether. When the glycopeptide antibiotic having a disaccharide group at A_4 is vancomycin, it is preferred that allyloxycarbonyl (aloc) groups are present on the amines of A_1 and the vancosamine residue, acetates on the aliphatic hydroxyl groups, allyl phenyl ethers on the phenolic hydroxyls, and an allyl or o-nitrobenzyl ester on the A_7 terminal carboxyl, where a solid-phase synthesis is employed, the o-nitrobenzyl ester is preferred. A degradation reaction then proceeds which remove a glycosidic group to produce a pseudoaglycone in which all reactive functional groups (amine, carboxylic acid, phenols, and benzylic alcohols) are suitably protected except for a hydroxyl group on the remaining glycosidic group attached to residue A_4 which is where another glycosidic group can optionally be attached.

Pharmaceutical formulations of the compounds of the present invention are also a part of the present invention, as well as the use of the compounds and formulations thereof to treat infectious diseases in mammals, preferably humans, comprising administering an amount of the

compound of the present invention or a pharmaceutically acceptable salt or ester thereof to a mammal, the amount being effective to treat the infectious disease.

Thus, the compounds of the present invention, or pharmaceutically acceptable salts or esters thereof can be formulated for any conventional means of delivery, including oral or parenteral delivery for the therapeutical or prophylactic treatment of infectious diseases, preferably bacterial diseases. The bacterial diseases which may be therapeutically or prophylactically treated with the compounds and/or formulations of the present invention include those caused by Gram-positive and/or Gram-negative microorganisms.

The compounds of the present invention may be administered separately or in combination with any other drug or therapeutic agent. Examples of other therapeutic agents and/or drugs that can be administered with the compounds and/or formulations of the present invention include, but are not limited to, beta lactam antibiotics, such as penems, penams, cephems, carbapenems, oxacephems, carbacephems, and monobactams, or other antibiotics such as cycloserine and fosfomycin. The other therapeutic agent need not be an antibiotic.

The compounds and/or formulations are administered to the mammal in a therapeutically effective amount, which amount is effective to treat, prevent, mitigate and/or alleviate the infectious disease. Thus, the compound of the present invention can be administered to the mammal, preferably a human, in an amount ranging from about 0.5 to about 2 grams per day. The compounds and/or formulations of the present invention can be administered in a single daily dosage or in multiple doses per day. Other periodic treatment protocols may also be adopted. Thus, the treatment protocol may require administration over extended periods of time, e.g., for several days or for from about one to six weeks. The therapeutically effective amounts of the compound of the invention discussed above are merely exemplary. Thus, the amount per

administered dose or the total amount administered will depend on such factors as the nature and severity of the infection, the age and general health of the patient, the tolerance of the patient to the compounds and/or formulations of the present invention and the microorganism or microorganisms involved in the infection.

In the pharmaceutical formulations of the present invention, the compound can be admixed with any conventional pharmaceutical carriers and/or excipients and can be formulated for immediate or sustained release. Other time-release profiles, such as combinations of immediate and sustained release are also possible. Thus, the compound of the present invention can be admixed with conventional pharmaceutical carriers and excipients and used in the form of tablets, capsules, caplets, elixirs, suspensions, syrups, wafers and the like. The compounds of the present invention can also be formulated for topical administration. Typical excipients and/or carriers include, but are not limited to corn starch, gelatin, lactose, sucrose, microcrystalline cellulose, kaolin, mannitol, dicalcium phosphate, sodium chloride, and alginic acid. Disintegrators commonly used in the formulations of this invention include croscarmellose sodium, microcrystalline cellulose, corn starch, sodium starch glycolate and alginic acid. Tablet binders that can be included are acacia, methylcellulose, polyvinylpyrrolidone, hydroxypropyl methylcellulose, sucrose, starch and ethylcellulose. Lubricants that can be used include magnesium stearate or other metallic stearates, stearic acid, silicone fluid, talc, waxes, oils and colloidal silica. Flavoring agents such as peppermint, oil of wintergreen, cherry flavoring or the like can also be used. It may also be desirable to add a coloring agent to make the dosage form more esthetic in appearance or to help identify the product. Tablets may be coated to facilitate swallowing or to modify release of the active compound, or some combination of these.

The compounds and/or formulations can also be administered intravenously or

intramuscularly. For intravenous (IV) use, a water-soluble form of the compound is preferably dissolved in one of the commonly used intravenous fluids, and administered by infusion. Such fluids as, for example, physiological saline, Ringer's solution or 5% dextrose can be used. For intramuscular preparations, a sterile formulation of a suitable salt or ester form of the compound of the present invention, for example the hydrochloride salt form can be dissolved and administered in a pharmaceutical diluent such as water-for-injection, physiological saline or 5% glucose solution. A suitable insoluble form of the compound may be prepared and administered as a suspension in an aqueous base or a pharmaceutically acceptable oil base, such as an ester of a long chain fatty acid such as ethyl oleate.

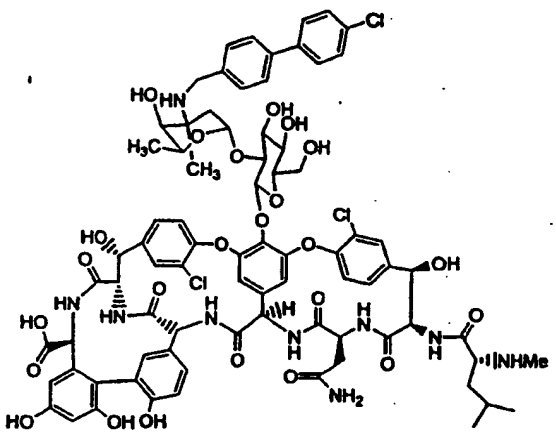
For oral use, a sterile formulation of a suitable salt or ester form of the compound, for example, the hydrochloric acid salt, formulated in a diluent such as distilled or deionized water is particularly useful. Alternatively, the unit dosage form of the compound can be a solution of the compound, preferably in its salt or ester from, in a suitable diluent in sterile, hermetically sealed ampoules.

EXAMPLES

The present invention will now be described with reference to the specific examples below, to which the present invention is not to be construed as limited to.

Example 1 - p-chlorobiphenyl vancomycin

The structural formula of p-chlorobiphenyl vancomycin is shown below:



chlorobiphenyl vancomycin
$C_{79}H_{84}Cl_3N_9O_{24}$
Exact Mass: 1647.47
Mol. Wt.: 1649.92

To a solution of vancomycin hydrochloride (20 mg; 13 μmoles) in 1.5 mL DMF was added diisopropylethylamine (11μL, 65 μmoles) and 4,4'-chlorobiphenylaldehyde (280 μL of a 10 mg/mL solution in DMF; 13 μmoles). The reaction mixture was stirred at 60 °C for half an hour. Sodium cyanoborohydride (77 μL of a 0.5M solution in DMF) was added, and the system was stirred at 60 °C for 1 hour.

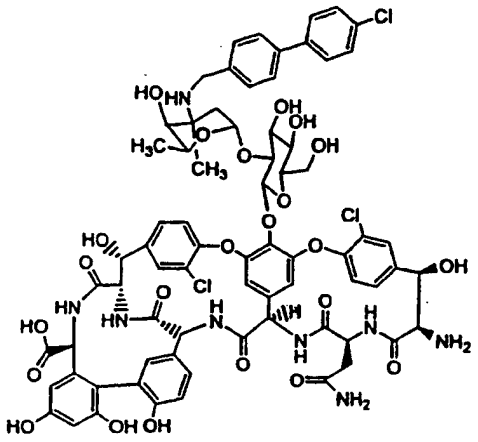
The reaction mixture was cooled to room temperature and diluted with 25 mL of ethyl ether. The precipitate was collected and purified by reverse phase HPLC:

HPLC conditions for product analysis:

Column:	Phenomenex C18 column, 21.2 x 250 mm
Flow:	8 mL/min
Mobile Phase:	B: acetonitrile
	4: 10 mM ammonium acetate, pH 5.2
Program:	0 min 30% B
	0.1 min 30% B
	25 min 55% B (linear gradient)
	35 min 90% B (linear gradient)
	35.5min 90% B (linear gradient)
	45 min 30% B

Example 2 - Des-leucyl p-chlorobiphenyl vancomycin (TS-518)

The structural formula of des-leucyl-p-chlorobiphenyl vancomycin is shown below:



Des-leucyl chlorobiphenyl vancomycin
$C_{72}H_{71}Cl_3N_8O_{23}$
Exact Mass: 1520.37
Mol. Wt.: 1522.73

Under an argon atmosphere, p-chlorobiphenyl vancomycin (130 mg, 7.8 μmoles) was dissolved in 3.4 mL of a 10:10:1 mixture of freshly distilled pyridine, distilled water and triethylamine (99%). Sonication was used to promoted total dissolution. To the colorless solution was added phenyl thioisocyanate (11μL, 90.1 μmoles), and the system was kept at 50 °C for 20 minutes. The slightly yellow solution was transferred to a separatory funnel, diluted with 10 mL of 10:10:1 pyridine-water-triethylamine solution, and washed with 10 mLof 10% ethyl acetate-hexane. The top layer was discarded. The yellowish bottom layer was transferred to a round-bottom flask, diluted with 5 mL of 2-butanol and concentrated to dryness. The residue was azeotroped twice with toluene. The resulting solid was dissolved in minimal amount of DMF (3

mL) and the product was precipitated by adding a large volume of 50% ethyl acetate-hexane (40 mL). The precipitate was collected by filtration, washed with methylene chloride (3 x 10 mL) and dried under vacuum to afford a nearly quantitative yield of des-leucyl p-chlorobiphenyl vancomycin (off-white solid). The product may be further purified by flash chromatography on silica gel (3:3:2 ethyl acetate-ethanol-water).

HPLC conditions for product analysis:

Column:	Nucleosil 4 C18 100 A (250 x 4.6 mm)
Flow:	0.75 mL/min
Mobile Phase:	B: acetonitrile
	5: 10 mM ammonium acetate, pH 5.2
Program:	0 min 25% B
	0.1 min 25% B
	20 min 40% B (linear gradient)
	30 min 90% B (linear gradient)
	30.1min 25% B (linear gradient)
	40 min 25% B

Retention time of product: 11.6 min.

Example 3

Compounds were typically prepared in batches of 48. To each of 48 test tubes was added the appropriate carboxylic acid (0.77 mmoles). Bis-(6-carboxy-HOBT)-N-(2-aminoethyl)-aminomethyl polystyrene resin (1.56 mmole/g; purchased from NovaBiochem; 1.19g) was suspended in 28 ml of amino-free DMF using mild, yet thorough, stirring. An aliquot of the suspension (500 µl) was added to each test tube, followed by 500 µL of amino-free DMF and 100 uL of a solution of 1,3-diisopropyl-carbodiimide in DMF (prepared by adding 750 µoL of 1,3-diisopropyl-carbodiimide to 5mL of amine-free DMF). The test tubes were shaken on an orbital shaker at 350 rpm for one hour. The supernatant was removed by filtration and discarded. The resin was washed with 2mL of amine-free DMF (6x).

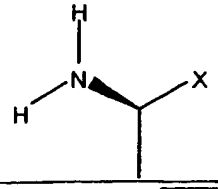
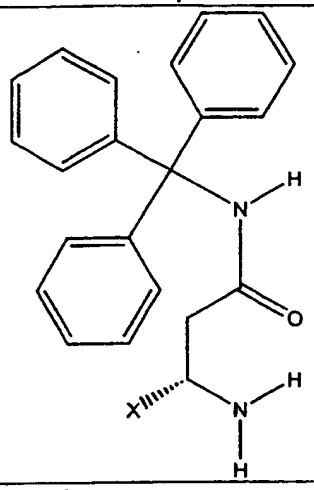
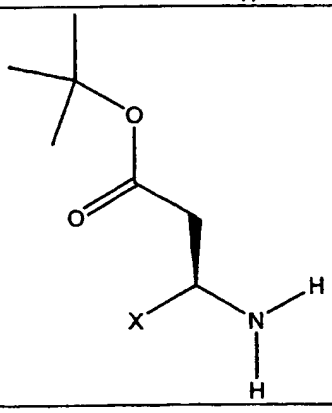
Des-(N-methyl-leucyl)-p-chlorobiphenyl-vancomycin (1.5g) was dissolved in 50 mL of amine-Free DMF using sonication. An aliquot of this solution (1 mL) was added to each test tube, followed by 1mL of amine-Free DMF. The test tubes were shaken on an orbital shaker at 350 rpm for one hour. The supernatant of each reaction mixture was transferred to the well of a labeled 48-well plate. The resin was washed with 1 mL of amine-free DMF (2x) and the washings were combined with the supernatant. In the cases where the carboxylic acid contained an Fmoc group, a 20% solution of piperidine in DMF (1 mL) was added to the corresponding well.

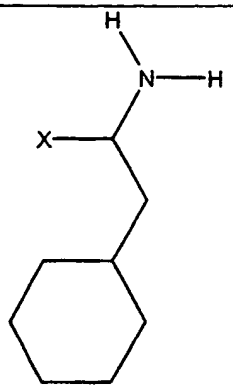
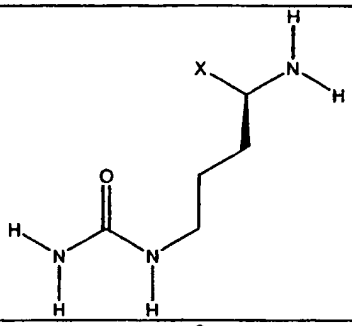
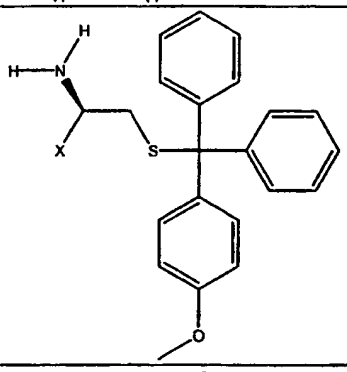
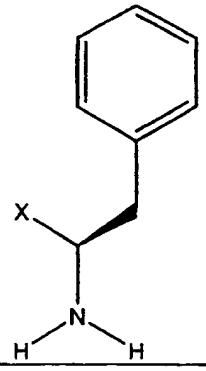
The plates were then dried in a centrifugal evaporator. The residues were treated with 5 mL of DMSO (molecular biology grade) and sonicated until total dissolution. The resulting solutions were used as such for analytical analysis and biological screening.

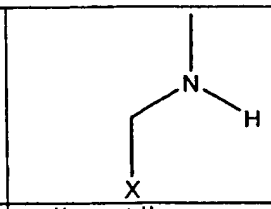
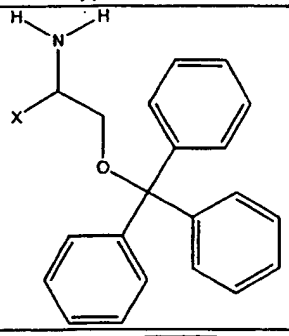
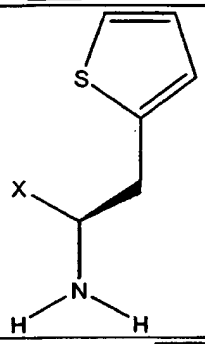
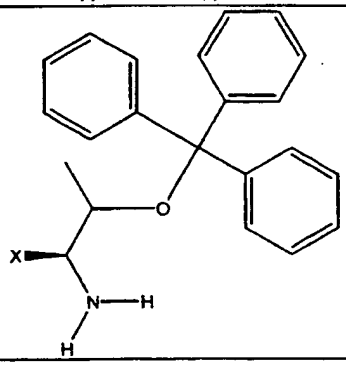
In the structural formulae in Table I below, "X" designates the -COOH group in the compound that is reacted with the free amino group at A_2, forming the new amide linkage.

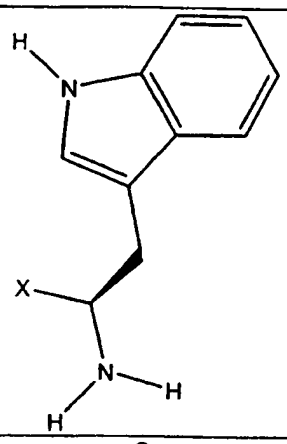
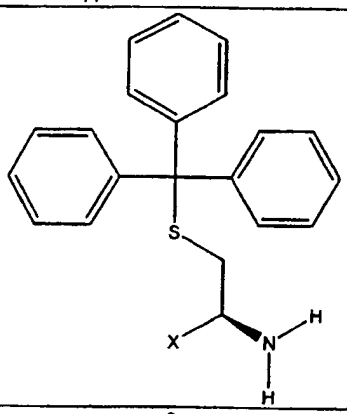
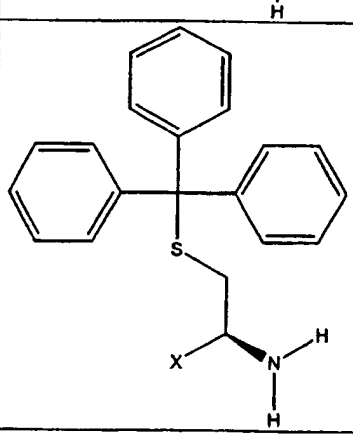
The antibacterial activity of each of the compounds against the bacterial strains *E. faceium* (ATCC 49624), *S. epidermidis* (ATCC 12228), *S. aureus* (ATCC 29213), *E. faecalis* (CL 4877) and *E. faecalis* (ATCC 292121) was tested. Each of the compounds was screened in a 96 wlll agar array format. Antibacterial activity was referenced to the zones of inhibition observed for p-chlorobiphenylvancomycin. The MIC's of p-chlorobiphenylvancomycin against resistant isolates were approximately 6 ug/ml. A zone score of 2 was assigned when the zone of inhibition for a given compound was equal to the zone generated by the delivery of a 1 mg/ml stock solution of p-chlorobiphenylvancomycin. A zone score of 1 was assigned if the area of the zone was 25% of the area of the zone generated by a 1 mg/ml stock solution of p-chlorobiphenylvancomycin. Likewise a zone score of 3 was assigned if the zone size was 4 times the size of the zone generated by a 1 mg/ml stock solution of p- chlorobiphenylvancomycin. Similarly, a zone score of 4 was assigned if the zone size was 16 times the size of the zone generated by a 1 mg/ml stock solution of p-chlorobiphenylvancomycin and a zone score of 5 was assigned if the zone size was 64 times the size of the zone generated by a 1 mg/ml stock solution of p-chlorobiphenylvancomycin. The screening data for each of the compounds is presented in Table I, below.

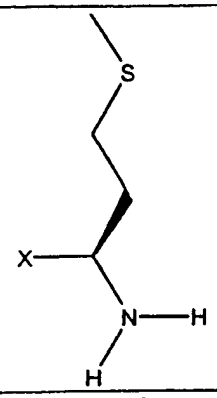
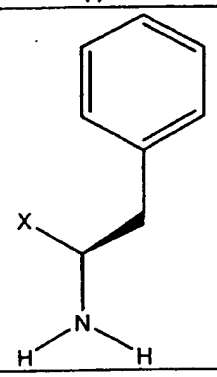
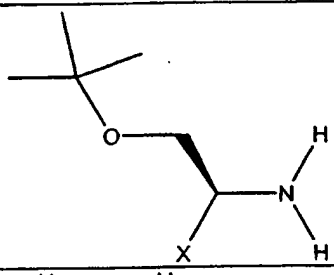
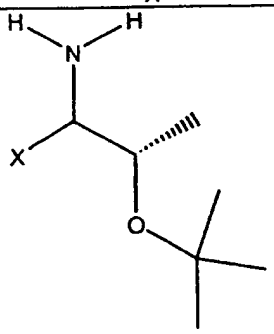
Table I – Side Chains attached to Free Amin Group at A_2 of des-leucyl -p-chlorobiphenyl vancomycin and Biological Screening Results

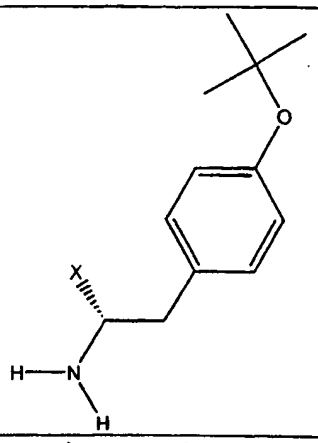
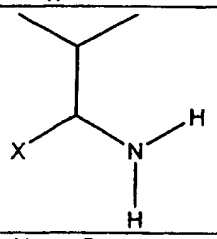
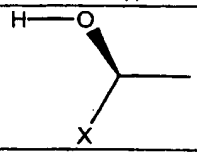
Cmpd No.		Reagent Name	*E. faecium* ATCC 49624	*S. epidermidis* ATCC 12228	*S. aureus* ATCC 29213	*E. faecalis* CL 4877	*E. faecalis* ATCC 29212
1		ALA	2	4	4	4	1
2		ASN(TRT)	1	1	1	2	1
3		ASP(OTBU)	1	3	2	2	1

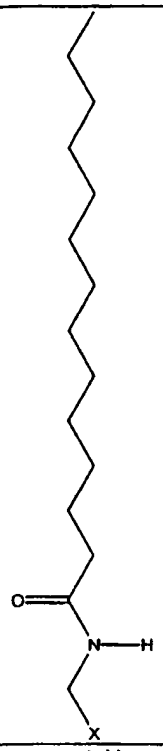
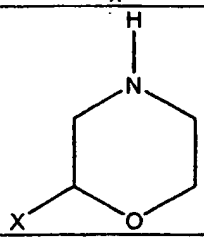
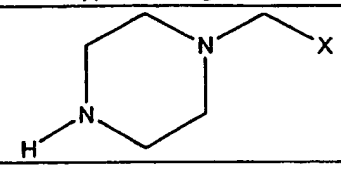
4		CHA	1	3	2	2	1
5		CIS	2	3	3	2	1
6		CYC(MMT)	1	1	1	2	1
7		PHE	1	3	2	2	1

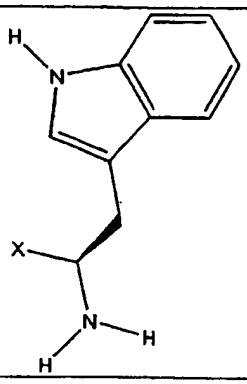
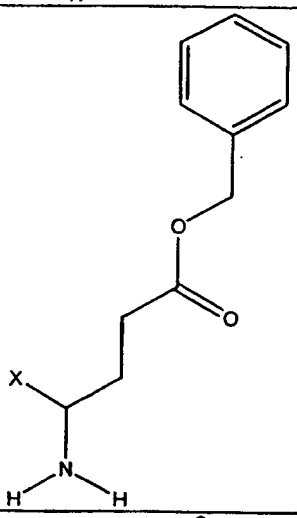
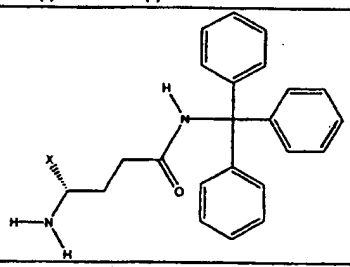
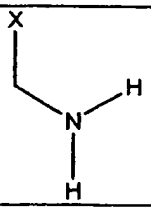
8		SAR	3	4	4	2	2
9		SER(TRT)	1	1	1	1	1
10		THI	2	3	2	3	1
11		THR(TRT)	1	1	1	2	1

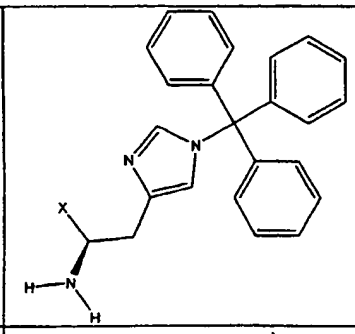
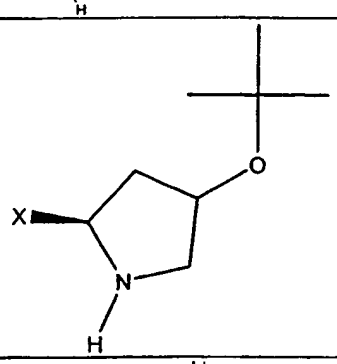
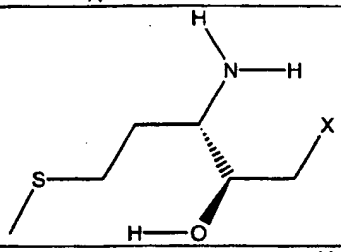
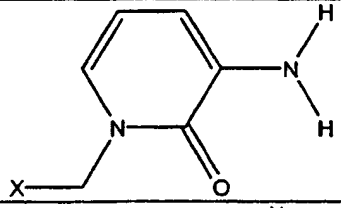
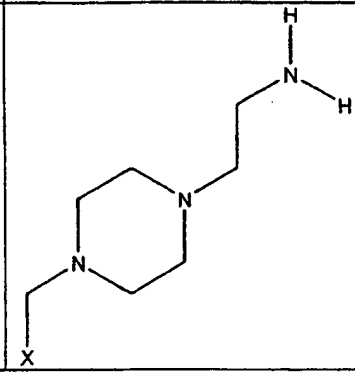
12		TRP	1	2	2	4	1
13		CYS(TRT)	1	1	1	1	1
14		D-CYS(TRT)	1	1	1	2	1

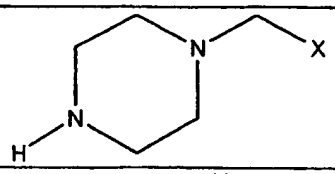
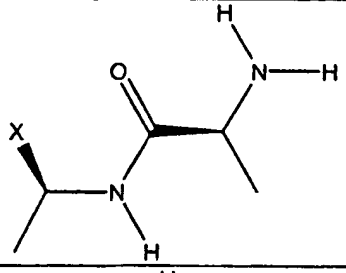
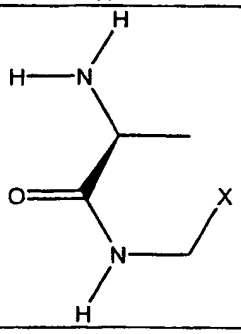
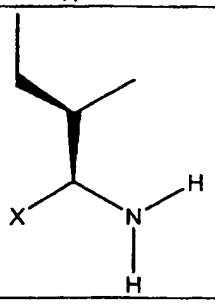
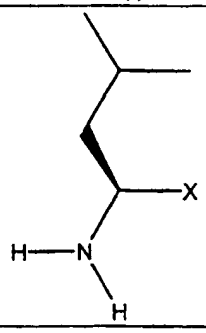
15		D-MET	4	5	5	2	4
16		D-PHE	3	5	4	3	3
17		D-SER(TBU)	5	5	5	5	5
18			2	3	2	3	1

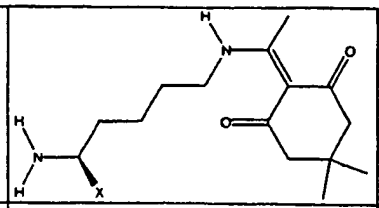
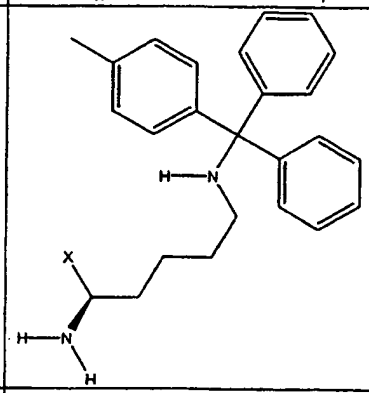
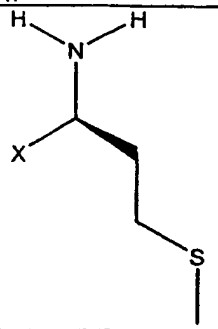
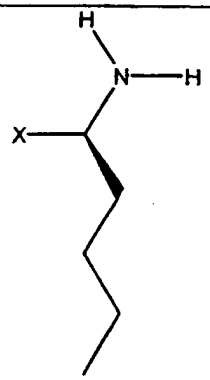
19		TYR(TBU)	1	3	2	3	1
20		VAL	2	4	3	4	1
21		L-(+)-LACTIC ACID	1	2	2	2	1

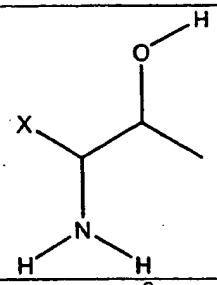
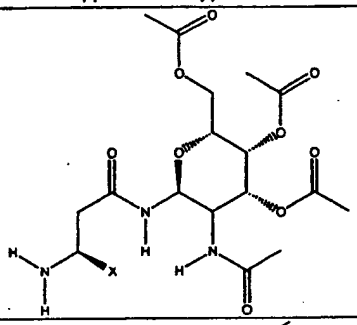
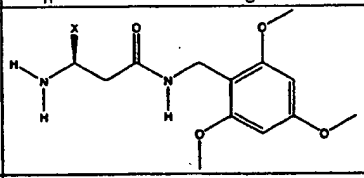
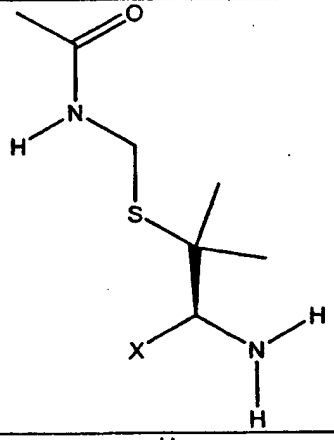
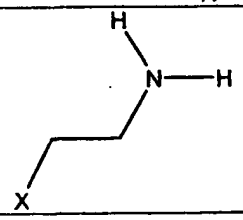
22		MYR-GLY	1	2	2	3	1
23		(R,S)-2-CARBOXY MORPHOLINE	1	2	2	2	1
24		4-PIPERAZIN-1-YL ACETIC ACID	2	2	3	4	1

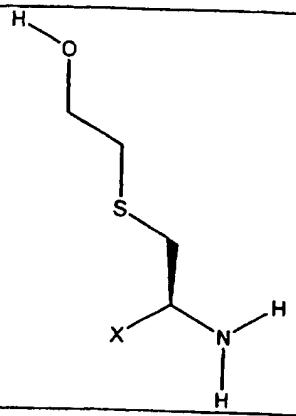
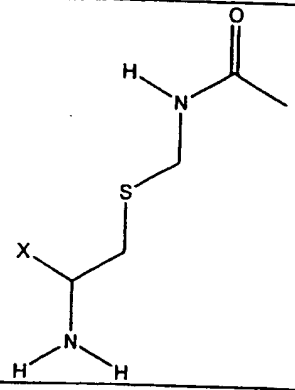
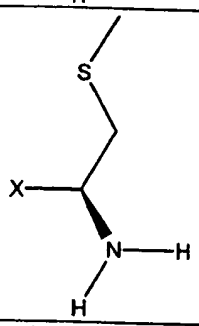
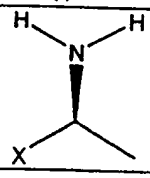
25		D-TRP	2	4	2	2	2
26		GLU(OBZL)	1	3	2	2	1
27		GLN(TRT)	1	1	1	3	1
28		GLY	2	4	3	2	2

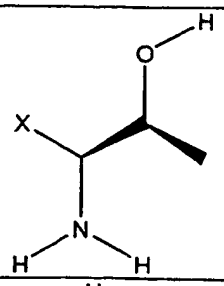
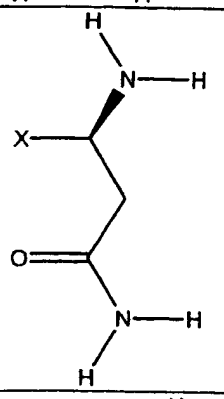
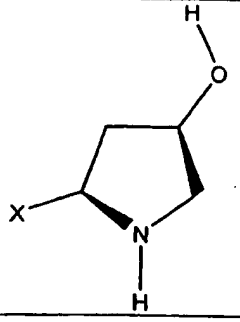
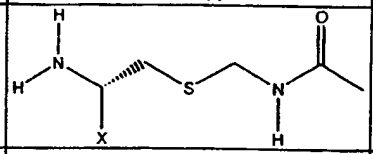
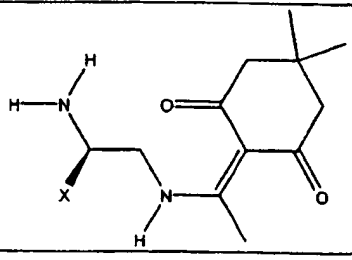
29		HIS(TRT)	1	1	1	1	1
30		HYP(TBU)	2	4	3	5	1
31		(3S,4S)-4-AMINO-3-HYDROXY-6-METHYLTHIO-HEXANOIC ACID	1	2	2	1	1
32		3-AMINO-1-CARBOXY METHYL-PYRIDIN-2-ONE	2	3	2	2	1
33		4-(2-AMINOETHYL)-1-CARBOXY METHYL-PIPERAZINE DIHYDRO CHLORIDE	2	3	2	2	1

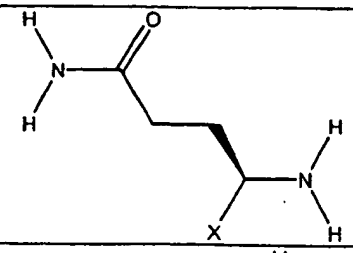
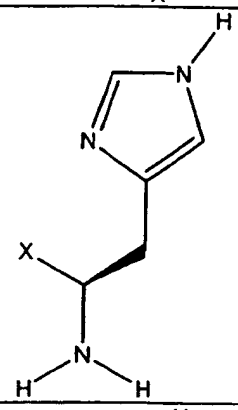
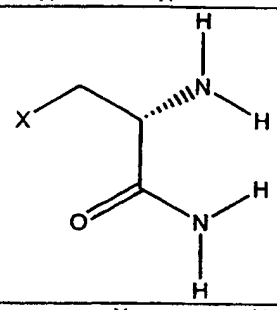
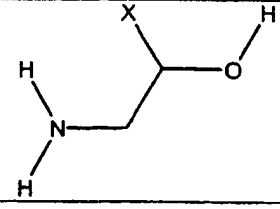
34		2-CARBOXY METHYL-PIPERAZINE	2	3	4	5	1
35		ALA-ALA	1	2	2	2	1
36		ALA-GLY	2	4	4	5	1
37		ILE	1	3	3	5	1
38		LEU	2	4	2	1	1

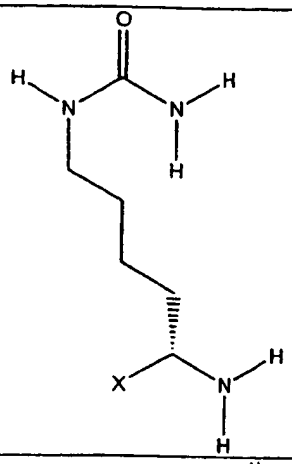
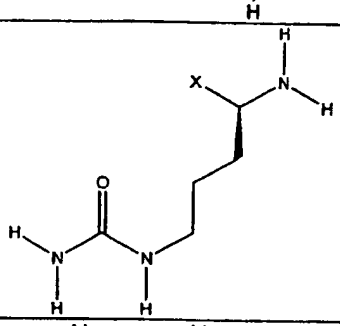
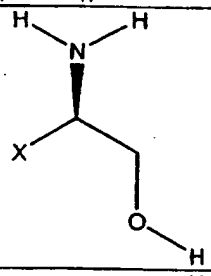
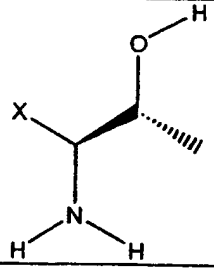
39		LYS(DDE)	1	3	2	2	1
40		LYS(MTT)	1	1	1	2	1
41		MET	2	4	3	2	1
42		NLE	2	4	4	5	1

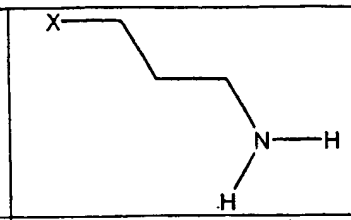
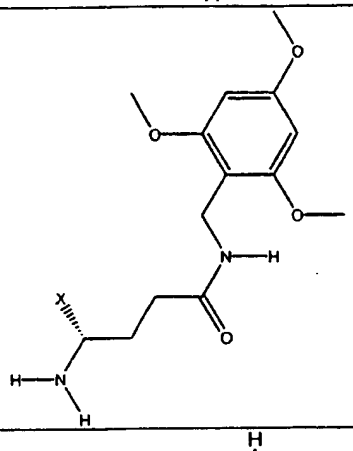
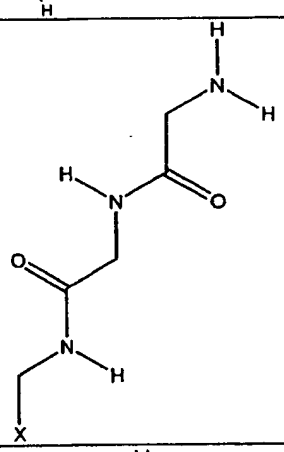
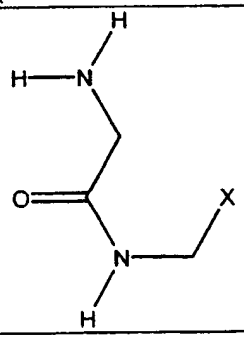
43		ALLO-THR	2	3	4	2	1
44		ASN(GLCNAC(AC)3-BETA-D)	1	1	1	1	1
45		ASN(TMOB)	1	2	2	2	1
46		BETA,BETA-DIMETHYL-D-CYS(ACM)	4	5	5	2	4
47		BETA-ALA	2	4	3	2	1

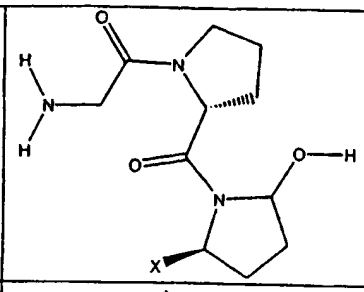
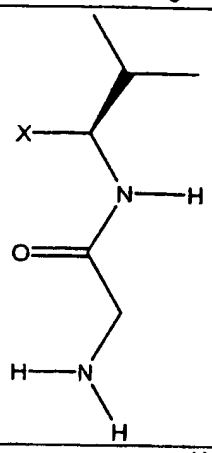
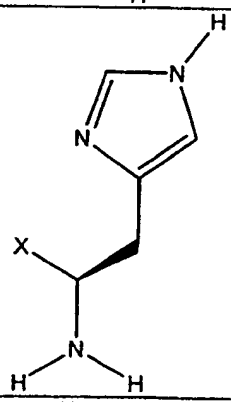
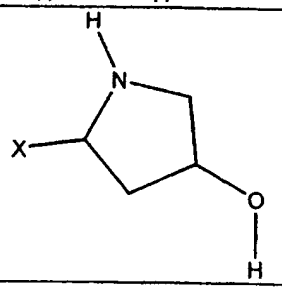
48		CYS(2-HYDROXY ETHYL)	1	2	2	2	1
49		CYS(ACM)	1	4	2	2	1
50		CYS(ME)	2	4	1	2	1
51		D-ALA	4	5	5	2	4

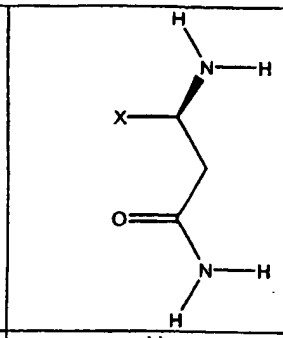
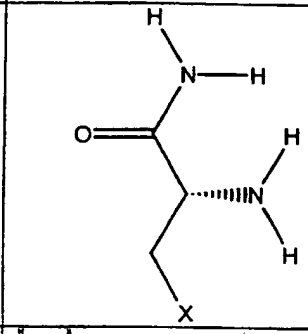
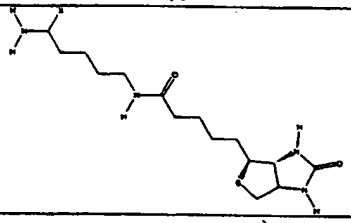
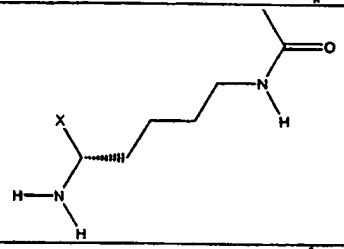
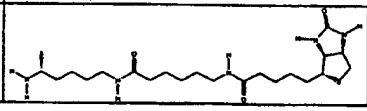
52		D-ALLO-THR	3	4	4	1	1
53		D-ASN	1	2	4	2	1
54		D-CIS-HYP	1	2	2	2	1
55		D-CYS(ACM)	3	4	4	2	1
56		D-DPR(DDE)	2	4	3	3	1

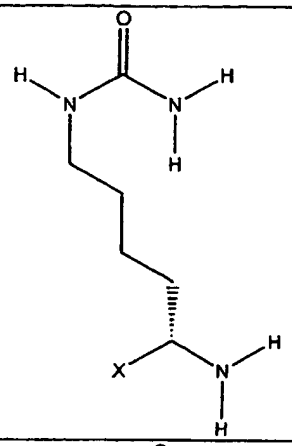
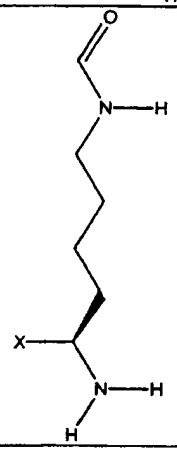
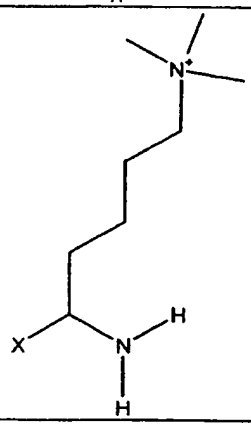
57		D-GLN	2	4	3	3	2
58		D-HIS	1	1	1	2	1
59		D-ISO ASPARAGINE	1	2	2	2	1
60		DL-ISOSER	1	1	1	2	1

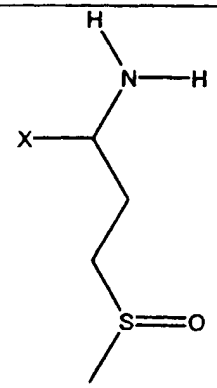
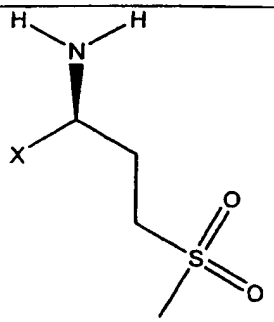
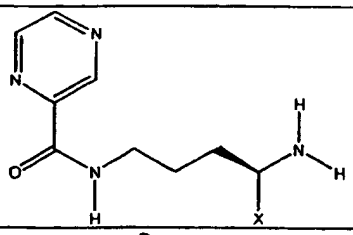
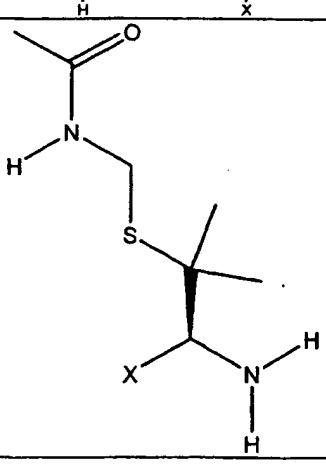
61		D-LYS (CARBAMYL)	4	5	5	3	4
62		D-ORN (CARBAMYL)	4	5	4	4	4
63		D-SER	3	4	2	2	1
64		D-THR	4	5	4	2	2

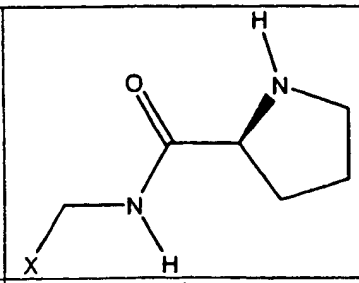
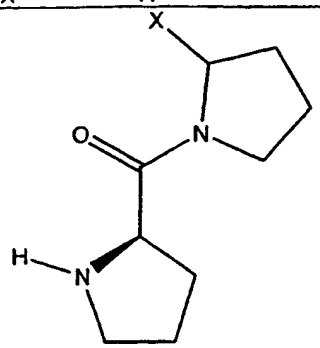
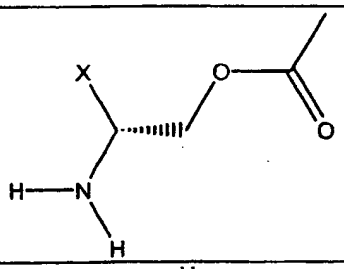
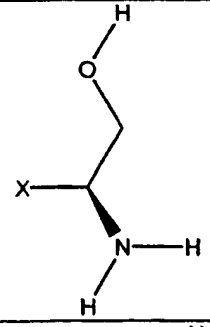
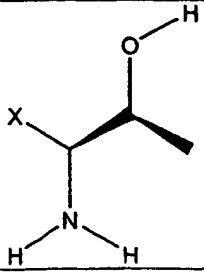
65		GAMMA-ABU	1	2	2	2	1
66		GLN(TMOB)	1	2	2	2	1
67		GLY-GLY-GLY	1	2	2	4	1
68		GLY-GLY	2	3	3	5	1

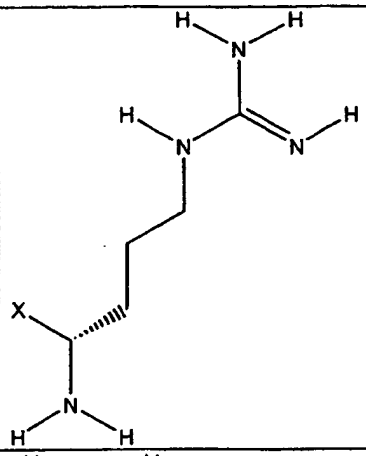
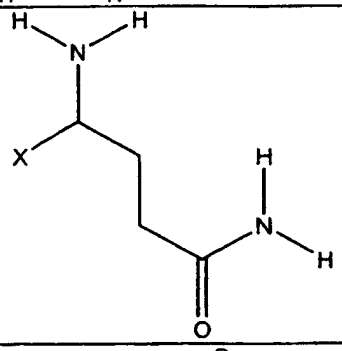
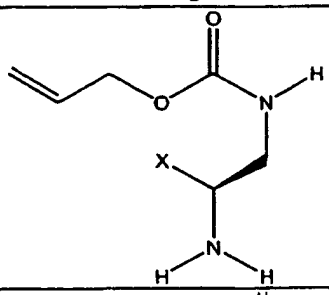
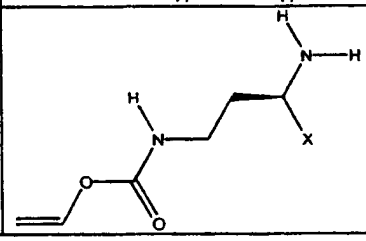
69		GLY-PRO-HYP	1	1	1	2	1
70		GLY-VAL	1	1	1	2	1
71		HIS	1	1	1	2	1
72		HYP	2	2	3	2	1

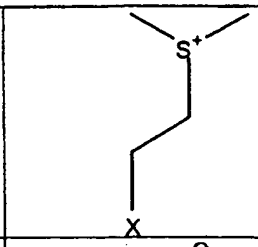
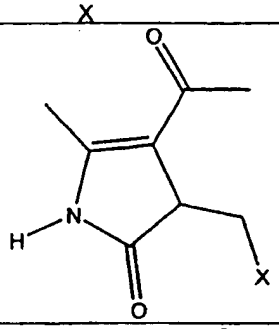
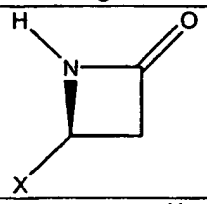
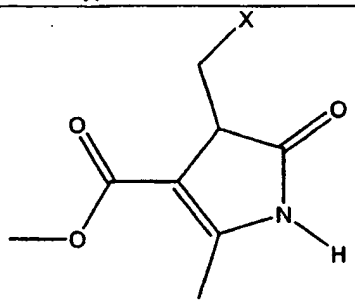
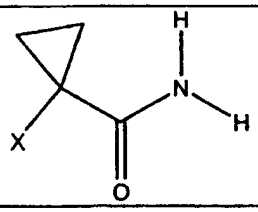
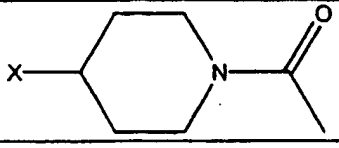
73		L-ASPARAGINE	1	1	1	1	1
74		L-ISO ASPARAGINE	1	2	2	1	1
75		L-LYS(BIOTIN)	2	2	1	2	2
76		LYS(AC)	2	2	1	1	1
77		LYS(BIOTINYL-EPSILON-AMINOCAPROYL)	1	1	1	5	1

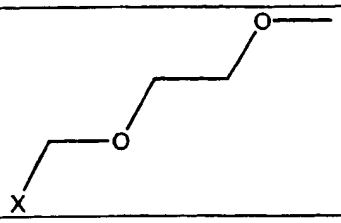
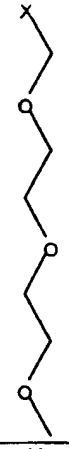
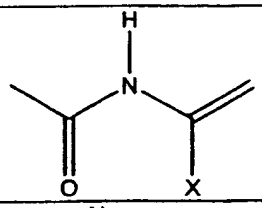
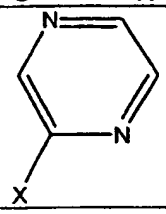
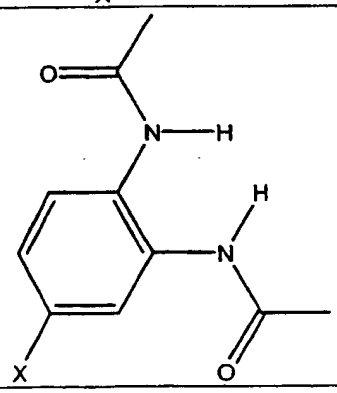
78		LYS(CARBAMYL)	1	2	2	1	1
79		LYS(FOR)	2	3	2	5	1
80		LYS(ME)3 CHLORIDE	2	4	2	5	1

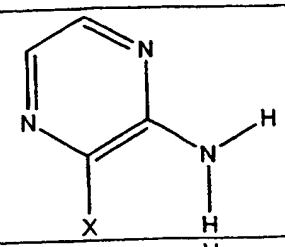
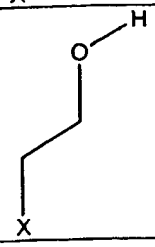
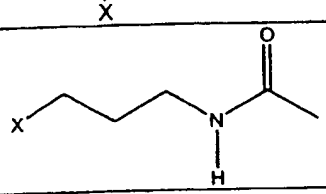
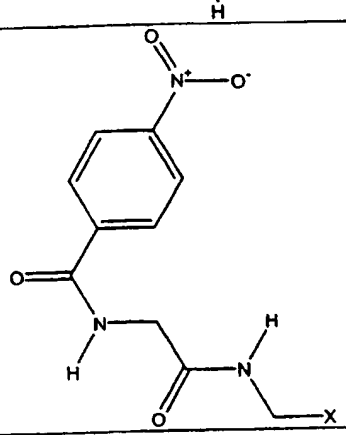
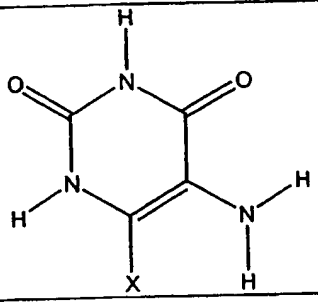
81		MET(O)	2	2	3	5	1
82		MET(O2)	2	3	3	4	1
83		ORN(PYRAZINYL CARBONYL)	2	3	2	4	1
84		PEN(ACM)	2	2	2	1	1

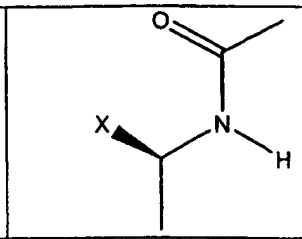
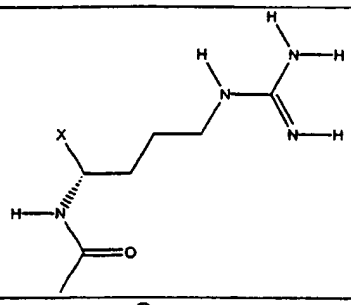
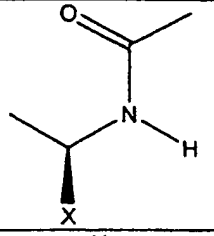
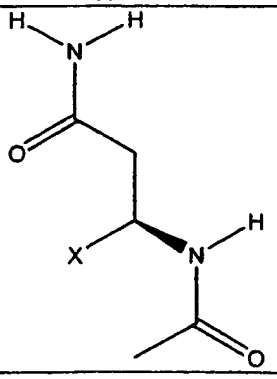
85		PRO-GLY	2	2	2	2	1
86		PRO-PRO	1	2	2	2	1
87		SER(AC)	1	2	2	2	1
88		SER	2	2	2	2	1
89		THR	2	2	1	2	1

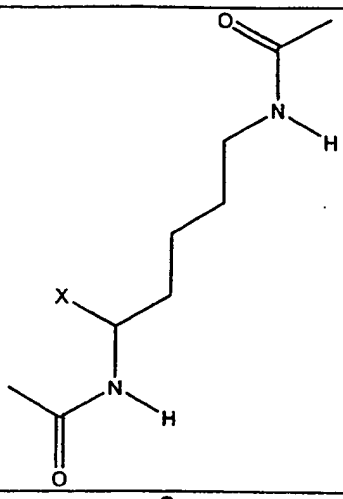
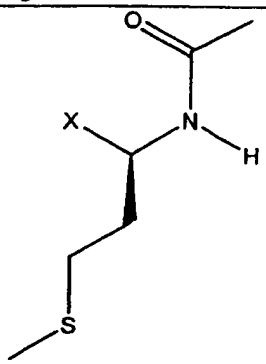
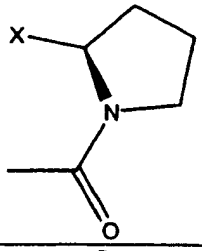
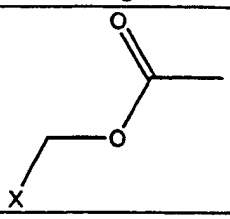
90		N-ALPHA-L-ARGININE	1	1	2	2	1
91		N-ALPHA-L-GLUTAMINE	1	2	3	5	1
92		N-ALPHA-N-BETA-ALOC-L-DIAMINO PROPIONIC ACID	1	3	3	2	1
93		N-ALPH-N-GAMMA-ALLOC-L-DIAMINO BUTYRIC ACID	1	2	2	3	1

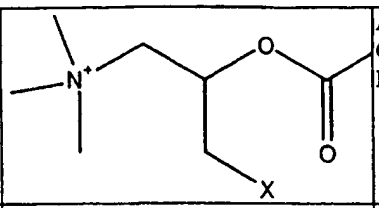
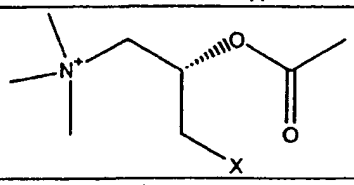
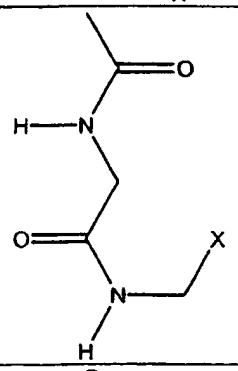
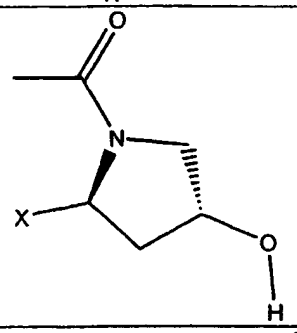
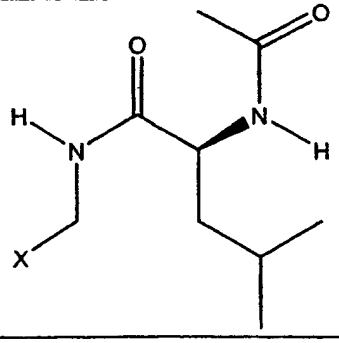
94		(2-CARBOXY ETHYL) DIMETHYL SULFONIUM CHLORIDE	1	2	2	2	1
95		(3-ACETYL-2-METHYL-5-OXO-2-PYRROLIN-4-YL) ACETIC ACID	1	1	1	3	1
96		(S)-(-)-4-OXO-2-AZETIDINE CARBOXYLIC ACID	1	1	1	2	1
97		[3-METHYOXY CARBONYL)-2-METHYL-5-OXO-2-PYRROLIN-4-YL]ACETIC ACID	1	1	1	1	1
98		1-(AMINO CARBONYL)-1-CYCLOPROPANE CARBOXYLIC ACID	1	1	2	2	1
99		1-ACETYL PIPERIDINE-4-CARBOXYLIC ACID	1	2	3	1	1

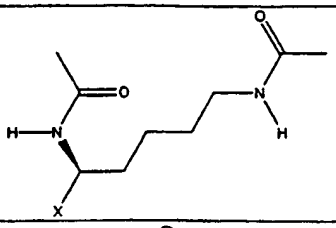
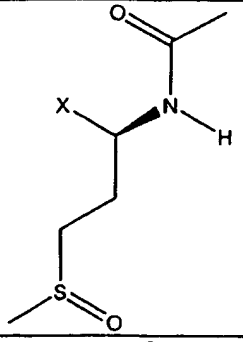
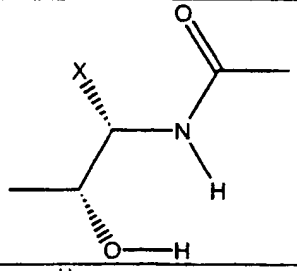
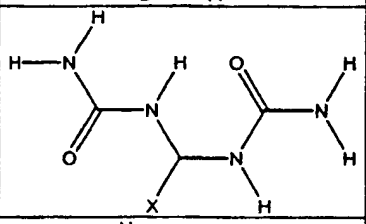
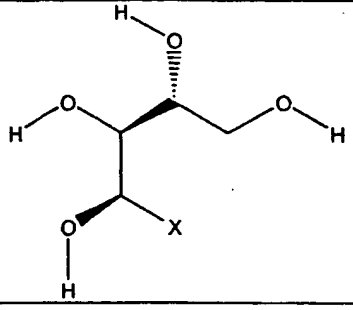
100		2-(2-METHOXY ETHOXY)ACETIC ACID	1	1	2	3	1
101		2-[2-(2-METHOXY ETHOXY) ETHOXY]ACETIC ACID	1	1	1	2	1
102		2-ACETAMIDO ACRYLIC ACID	1	1	1	2	1
103		2-PYRAZINE CARBOXYLIC ACID	1	1	1	2	1
104		3,4-DIACETAMIDO BENZOIC ACID	1	1	2	2	1

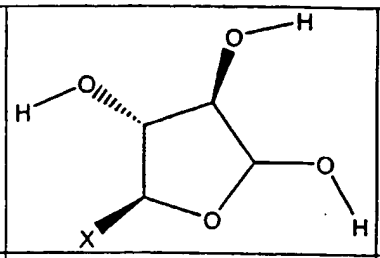
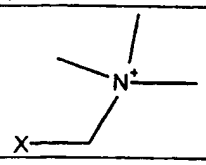
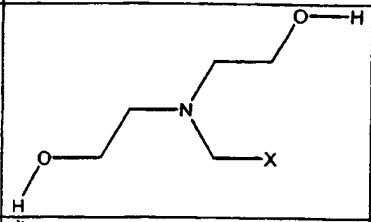
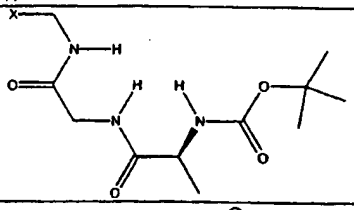
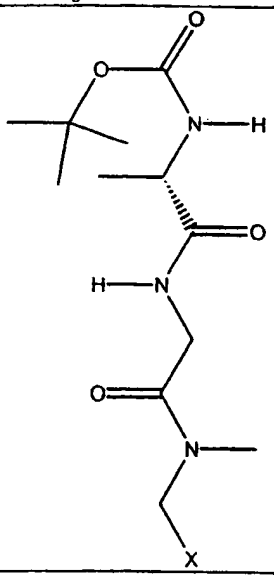
105		3-AMINO PYRAZINE-2-CARBOXYLIC ACID	1	1	1	2	1
106		3-HYDROXY PROPIONIC ACID	1	2	2	2	1
107		4-ACETAMIDO BUTYRIC ACID	1	1	2	2	1
108		4-NITRO BENZOYL-GLYCYL-GLYCINE	1	1	2	4	1
109		5-AMINOOROTIC ACID	1	1	2	1	1

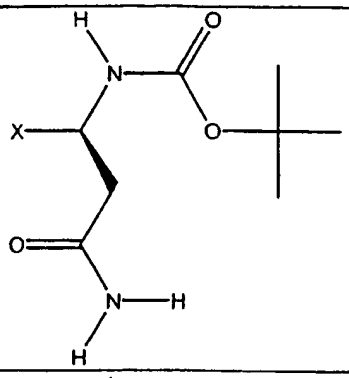
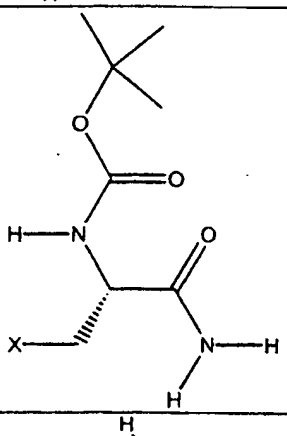
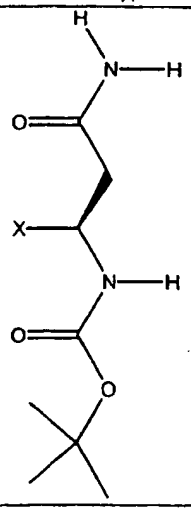
110		AC-ALA	1	1	2	2	1
111		AC-ARG	1	1	1	2	1
112		AC-D-ALA	1	1	2	4	1
113		AC-D-ASN	1	1	1	2	1

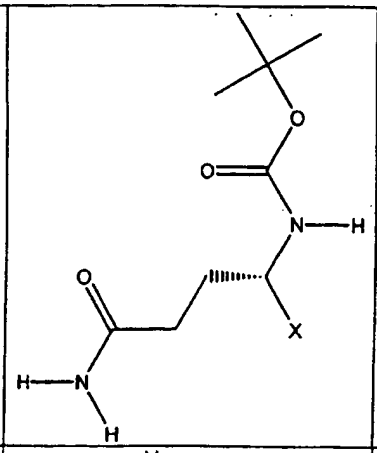
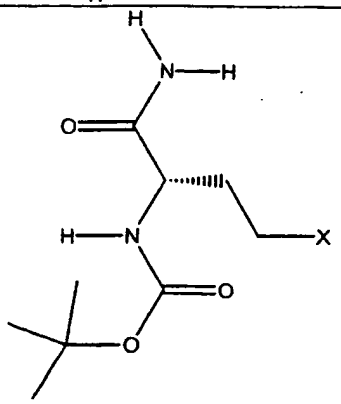
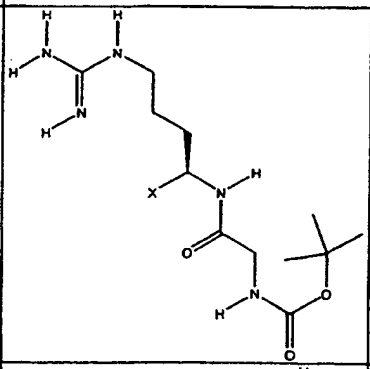
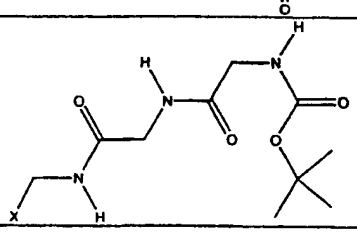
114		AC-DL-LYS(AC)	1	1	1	2	1
115		AC-D-MET	1	1	2	2	1
116		AC-D-PRO	1	2	2	2	1
117		ACETOXYACETIC ACID	1	2	2	1	1

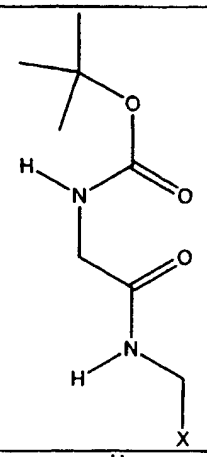
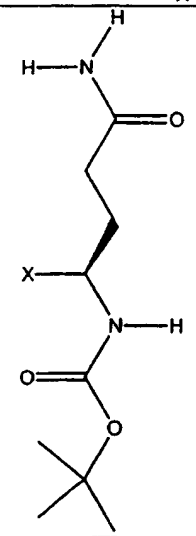
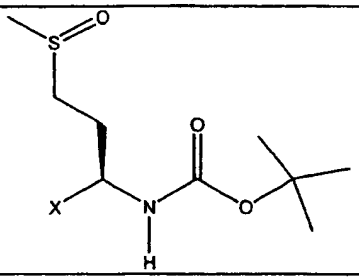
118		ACETYL-DL-CARNITINE HYDROCHLORIDE	1	2	2	4	1
119		ACETYL-L-CARNITINE-HYDROCHLORIDE	1	2	2	2	1
120		AC-GLY-GLY	1	2	2	2	1
121		AC-HYP	1	1	2	2	1
122		AC-LEU-GLY	1	1	1	1	1

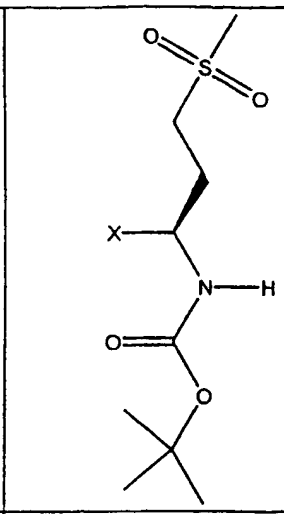
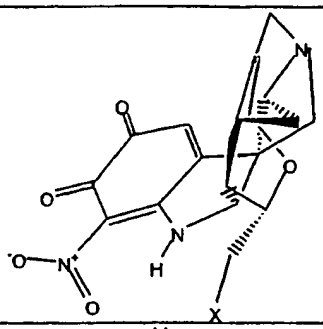
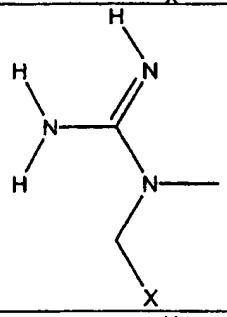
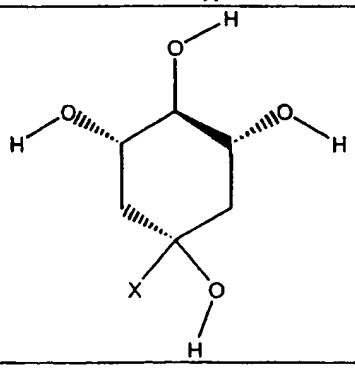
123		AC-LYS(AC)	1	1	2	1	1
124		AC-MET(O)	1	1	2	4	1
125		AC-THR	1	1	1	2	1
126		ALLANTOIC ACID	1	1	1	2	1
127		ARABIC ACID	1	1	1	2	1

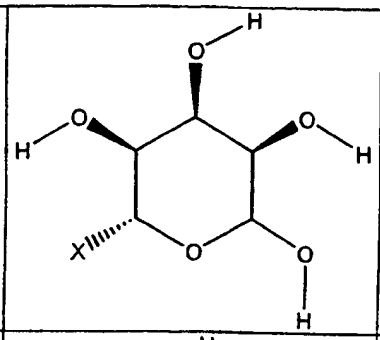
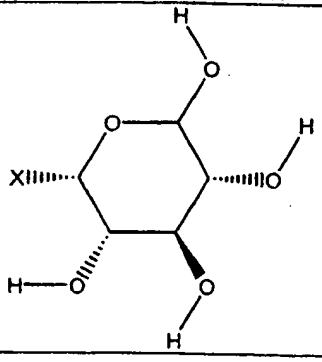
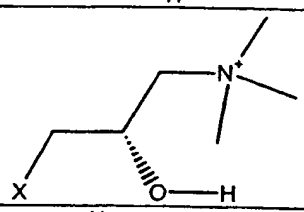
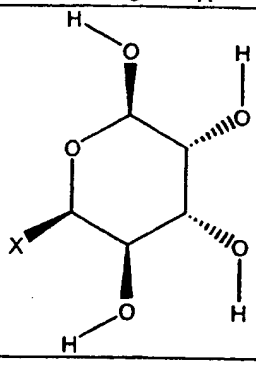
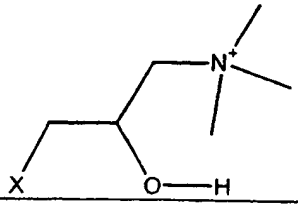
128		ARABINIC ACID	1	1	2	1	1
129		BETAINE HYDROCHLORIDE	1	2	1	2	1
130		BICINE	1	1	2	2	1
131		BOC-ALA-GLY-GLY	1	1	2	2	1
132		BOC-ALA-GLY-SAR	1	1	2	2	1

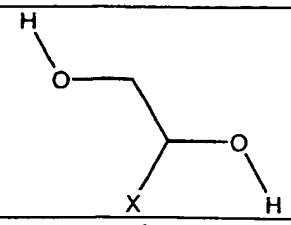
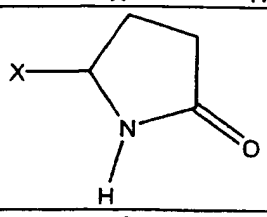
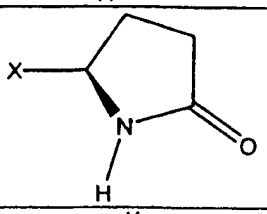
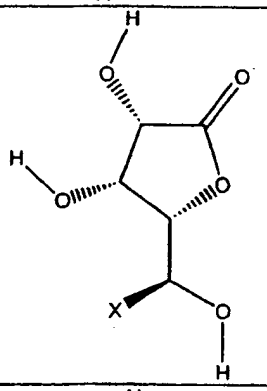
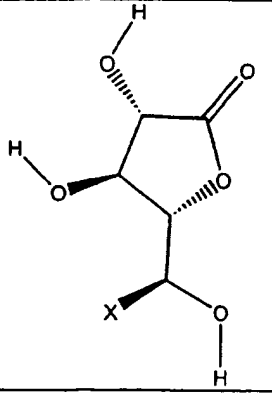
133		BOC-ASN	1	1	1	2	1
134		BOC-ASP-NH2	1	2	3	2	1
135		BOC-D-ASN	1	2	2	3	1

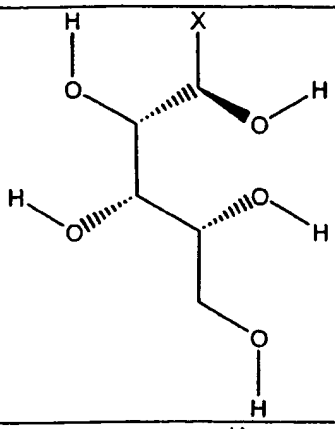
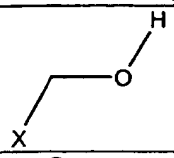
136		BOC-D-GLN	1	2	1	4	1
137		BOC-GLU-NH2	1	1	2	2	1
138		BOC-GLY-ARG	1	1	1	2	1
139		BOC-GLY-GLY-GLY	1	1	2	2	1

140		BOC-GLY-GLY	1	1	1	2	1
141		BOC-L-GLUTAMINE	1	1	2	2	1
142		BOC-MET(O)	2	1	2	2	1

143		BOC-MET(O2)	1	1	2	1	1
144		CACOTHELINE	1	1	1	2	1
145		CREATINE	1	1	1	2	1
146		D-(-)-QUINIC ACID	1	1	1	2	1

147		D-(+)-GALACTURONIC ACID MONOHYDRATE	1	1	1	2	1
148		D-ALPHA-GALACTURONIC ACID	1	1	1	2	1
149		D-CARNITINE HYDROCHLORIDE	2	1	1	2	1
150		D-GLUCURONIC ACID	1	1	1	1	1
151		DL-CARNITINE HYDROCHLORIDE	2	2	4	2	1

152		DL-GLYCERIC ACID	1	1	1	2	1
153		DL-PYRO GLUTAMIC ACID	1	1	1	1	1
154		D-PYRO GLUTAMIC ACID	1	1	1	1	1
155		D-SACCHARIC ACID 1,4-LACTONE	1	1	1	2	1
156		D-SACCHARIC ACID 3,6-LACTONE	1	1	1	1	1

157		GLUCONIC ACID	1	1	2	2	1
158		GLYCOLIC ACID	1	2	2	2	1
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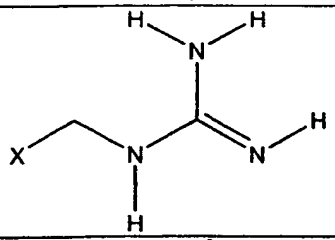
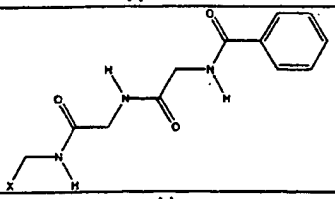
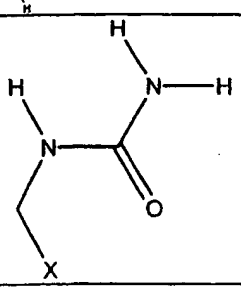
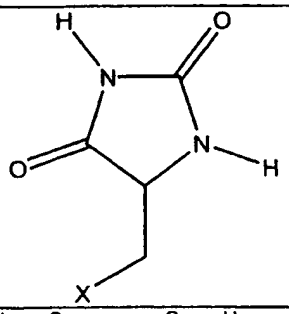
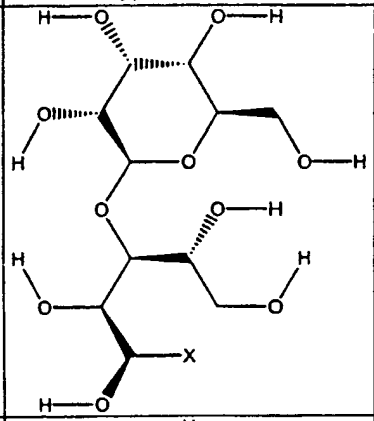
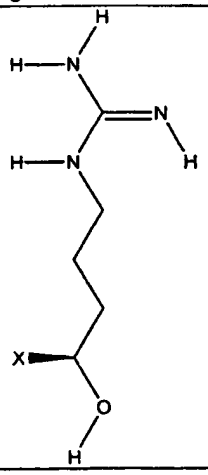
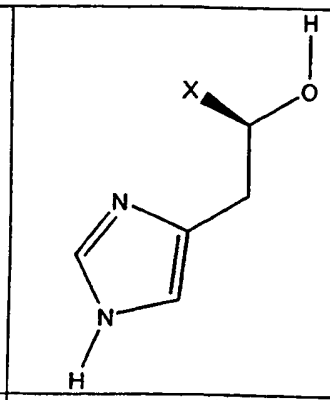
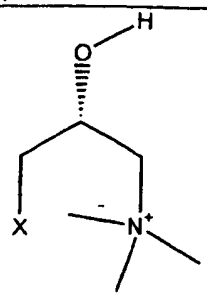
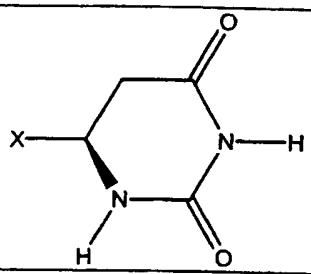
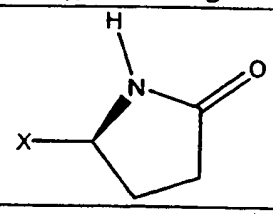
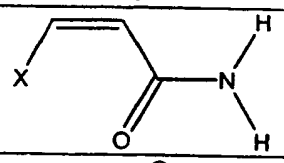
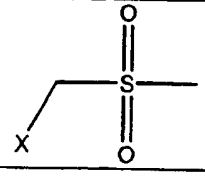
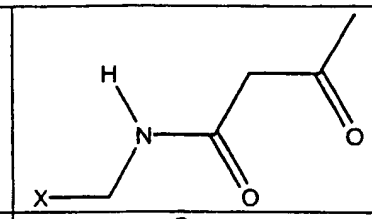
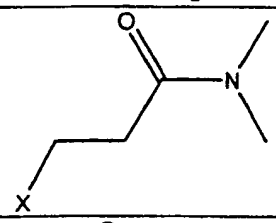
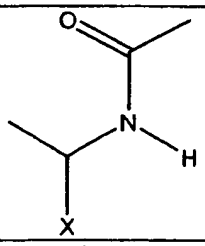
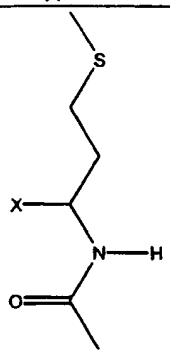
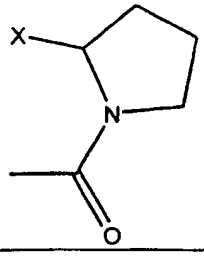
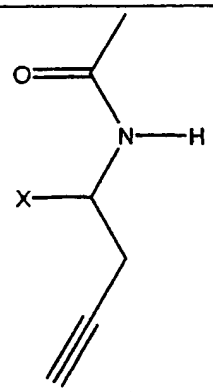
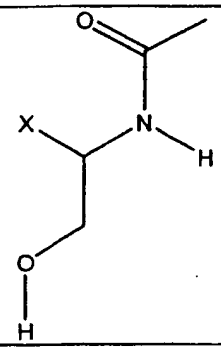
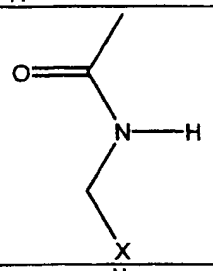
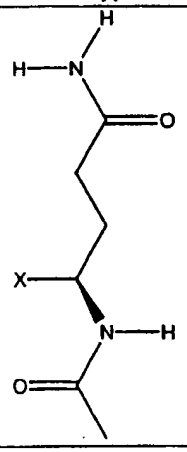
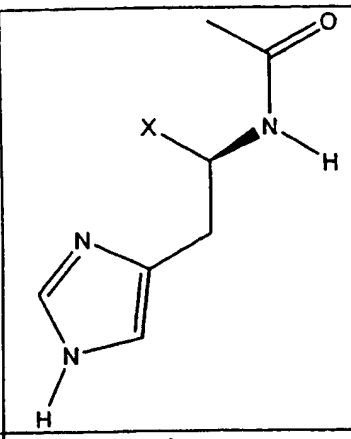
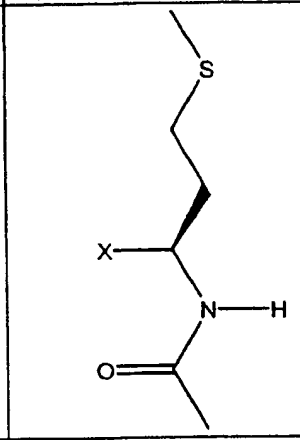
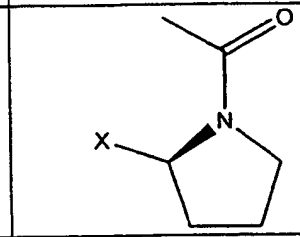
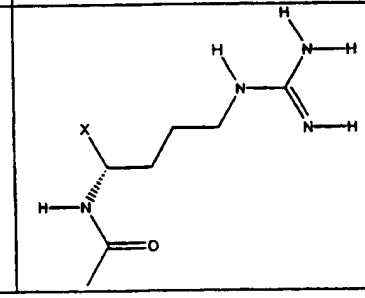
160		GUANIDOACETIC ACID	1	1	1	1	1
161		HIPPURYL-GLY-GLY-OH	1	1	1	2	1
162		HYDANTOIC ACID	1	1	1	2	1

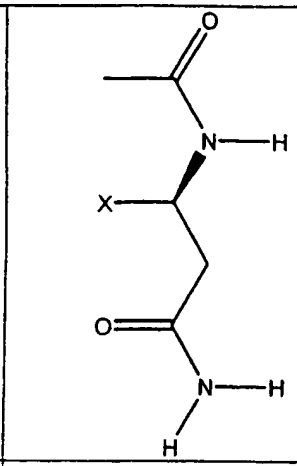
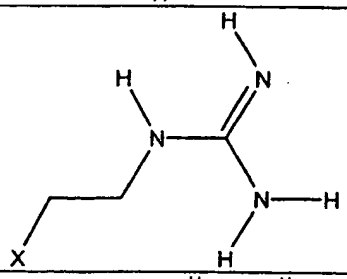
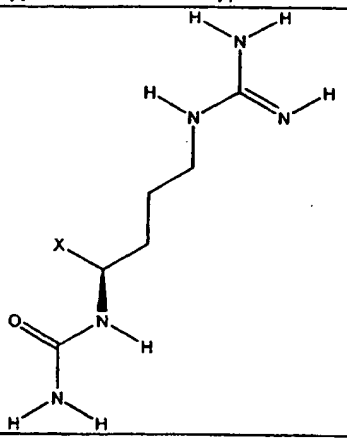
163		HYDANTOIN-5-ACETIC ACID	1	1	2	1	1
164		LACTOBIONIC ACID	1	1	1	1	1
165		L-ARGININIC ACID	1	1	1	2	1

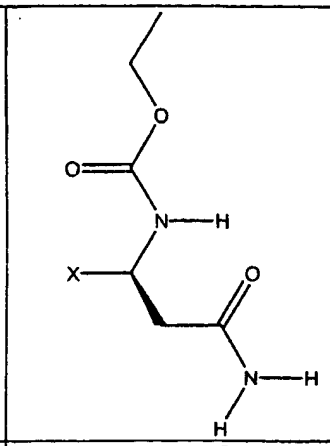
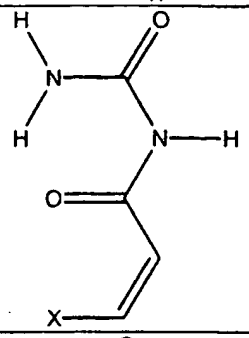
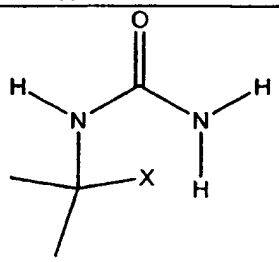
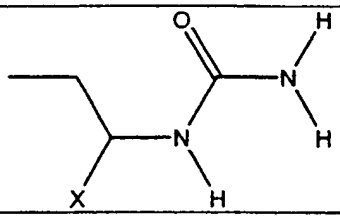
166		L-BETA-IMIDAZO LELACTIC ACID	1	1	1	1	1
167		L-CARNITINE HYDROCHLORIDE	1	1	1	1	1
168		L-DIHYDRO OROTIC ACID	1	1	1	2	1
169		L-PYRO GLUTAMIC ACID	1	1	1	2	1
170		MALEAMIC ACID	1	2	1	2	1
171		METHANE SULFONYL ACETIC ACID	1	1	1	2	1

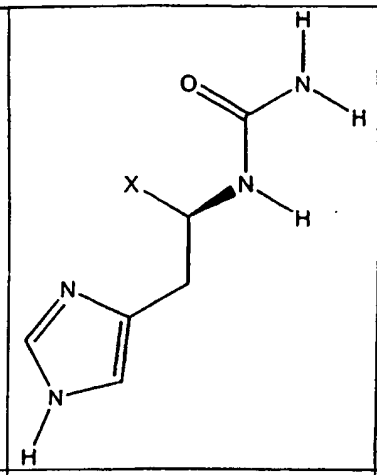
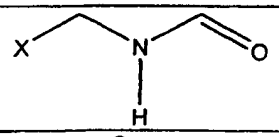
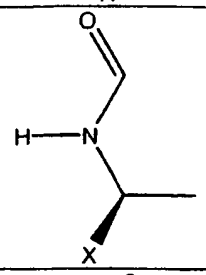
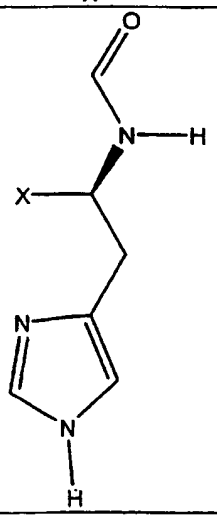
172		N-(ACETO ACETYL) GLYCINE	1	1	1	2	1
173		N,N-DIMETHYL SUCCINAMIC ACID	1	1	1	1	1
174		N-ACETYL-DL-ALANINE	1	1	1	2	1
175		N-ACETYL-DL-METHIONINE	1	2	2	1	1
176		N-ACETYL-DL-PROLINE	1	2	2	2	1

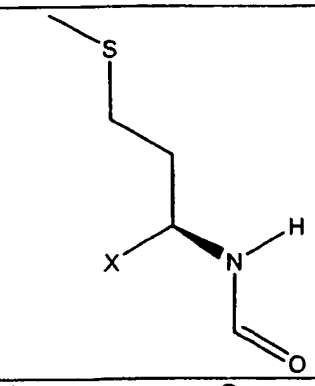
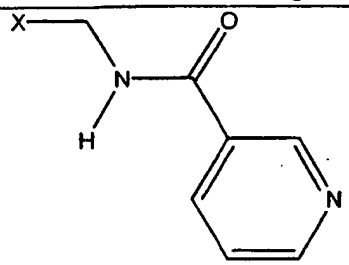
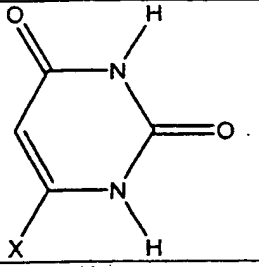
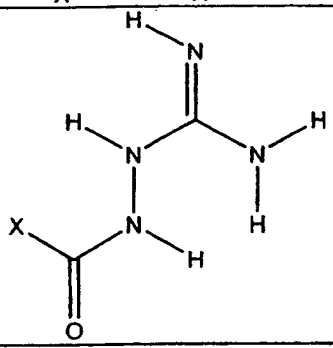
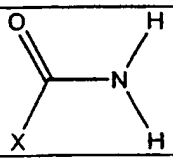
177		N-ACETYL-DL-PROPARGYL-GLYCINE	1	1	2	2	1
178		N-ACETYL-DL-SERINE	1	1	1	2	1
179		N-ACETYL GLYCINE	1	1	1	2	1
180		N-ACETYL-L-GLUTAMINE	1	1	1	1	1

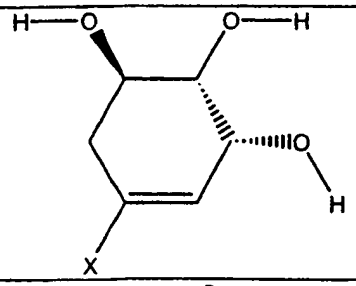
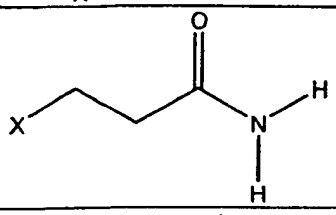
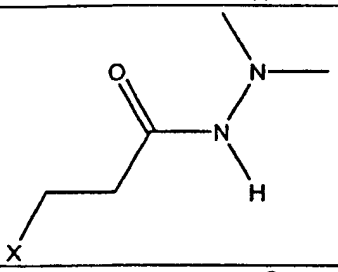
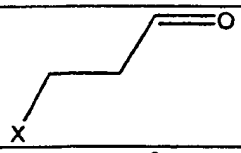
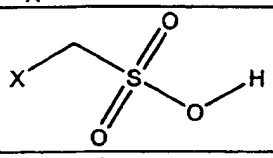
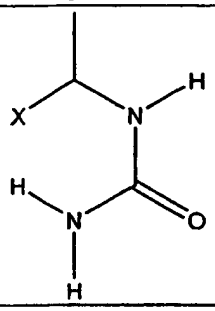
181		N-ACETYL-L-HISTIDINE	1	2	2	2	1
182		N-ACETYL-L-METHIONINE	1	2	1	2	1
183		N-ACETYL-L-PROLINE	1	2	2	2	1
184		N-ALPHA-ACETYL-L-ARGININE DIHYDRATE	1	1	1	2	1

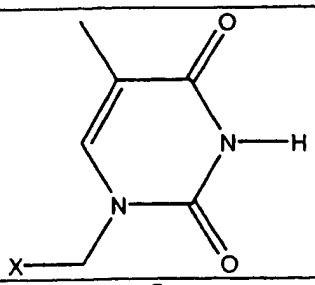
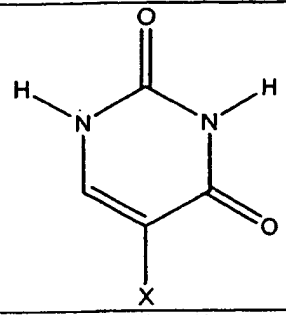
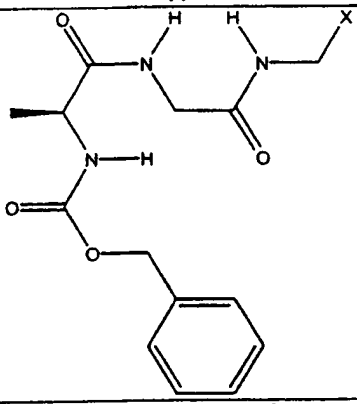
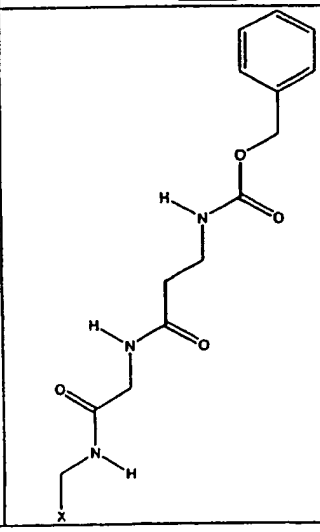
185		N-ALPHA-ACETYL-L-ASPARAGINE	1	1	1	1	1
186		BETA-GUANIDINO PROPIONIC ACID	1	1	1	1	1
187		N-ALPHA-CARBAMYL-L-ARGININE	1	1	2	2	1

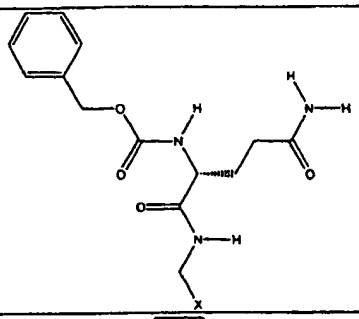
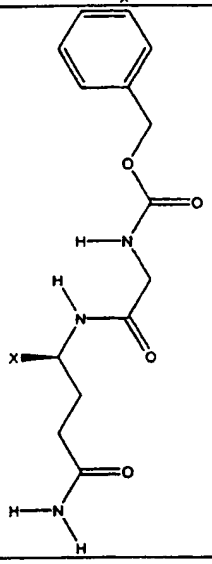
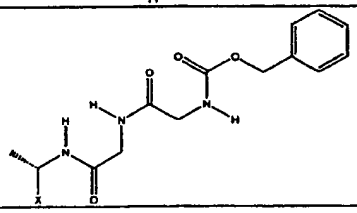
188		N-ALPHA-CARBOETHOXY-L-ASPARAGINE	1	1	2	2	1
189		N-CARBOMOYL MALEAMIC ACID	1	1	2	2	1
190		N-CARBAMYL-ALPHA-AMINO-ISOBUTYRIC ACID	1	1	2	3	1
191		N-CARBAMYL-DL-ALPHA-AMINO-N-BUTYRIC ACID	1	1	1	3	1

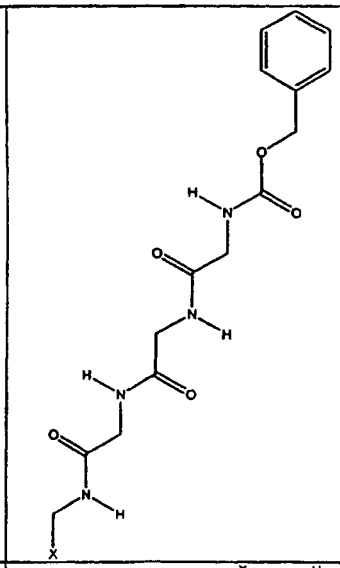
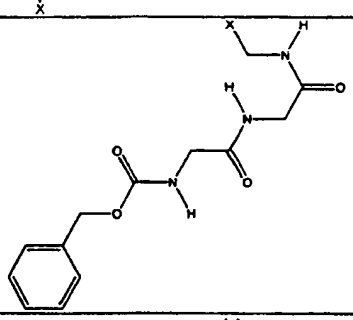
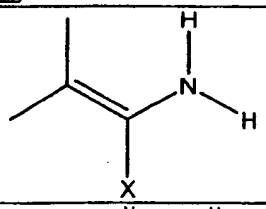
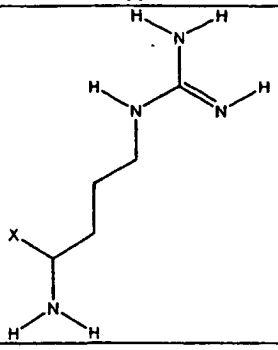
192		N-CARBAMYL-L-HISTIDINE HYDROCHLORIDE	1	1	1	2	1
193		N-FORMYL GLYCINE	1	2	3	2	1
194		N-FORMYL-L-ALANINE	1	1	2	2	1
195		N-FORMYL-L-HISTIDINE	1	2	2	2	1

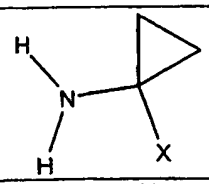
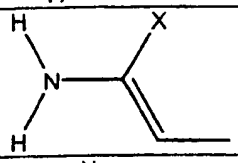
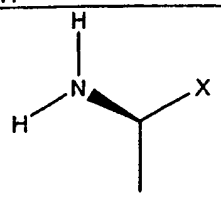
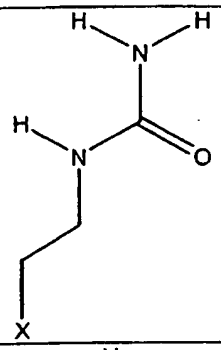
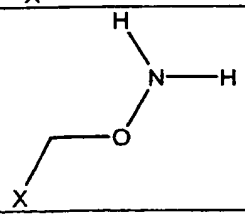
196		N-FORMYL-L-METHIONINE	1	1	2	3	1
197		NICOTINURIC ACID	1	1	2	2	1
198		OROTIC ACID	1	2	2	3	1
199		OXALYL MONOGUANYL HYDRAZIDE	1	1	2	2	1
200		OXAMIC ACID	1	1	2	2	1

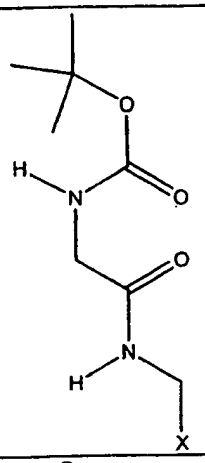
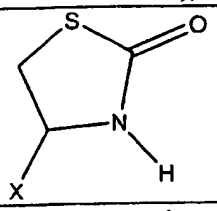
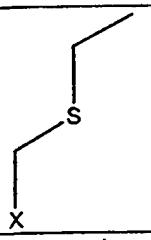
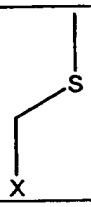
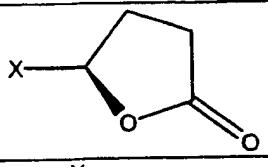
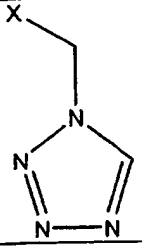
201		SHIKIMIC ACID	1	1	2	2	1
202		SUCCINAMIC ACID	1	2	2	2	1
203		SUCCINIC ACID 2,2-DIMETHYL HYDRAZIDE	1	1	2	1	1
204		SUCCINIC SEMIALDEHYDE	1	1	2	2	1
205		SULFOACETIC ACID	1	1	2	2	1
206		DL-2-UREIDO PROPIONIC ACID	1	2	2	2	1

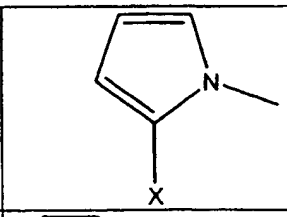
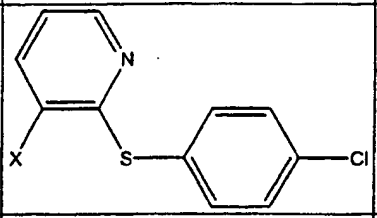
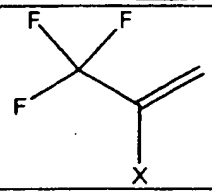
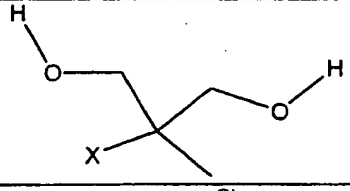
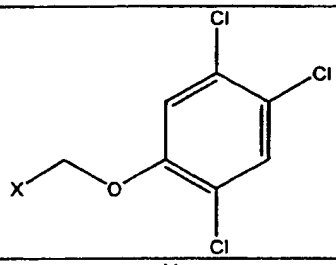
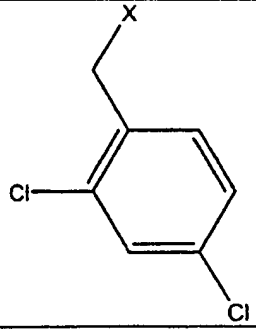
207		THYMINE-1-ACETIC ACID	1	2	4	3	1
208		URACIL-5-CARBOXYLIC ACID	1	1	2	2	1
209		Z-ALA-GLY-GLY	1	2	2	2	1
210		Z-BETA-ALA-GLY-GLY	1	2	2	2	1

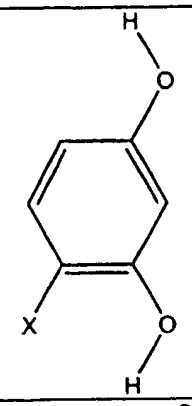
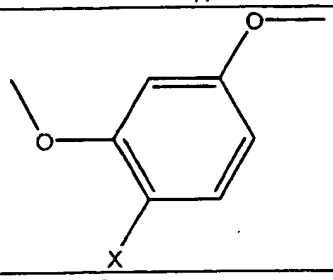
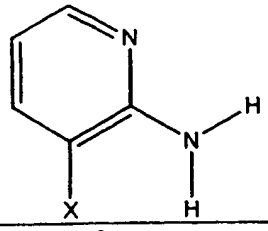
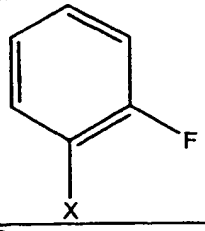
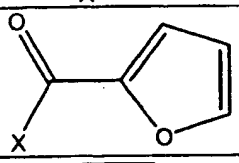
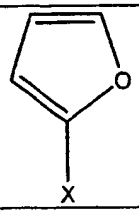
211		Z-GLN-GLY	1	2	2	2	1
212		Z-GLY-GLN	1	2	2	2	1
213		Z-GLY-GLY-ALA	1	2	2	2	1

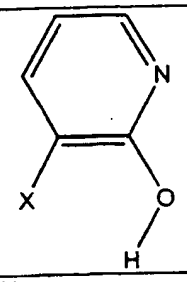
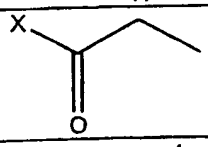
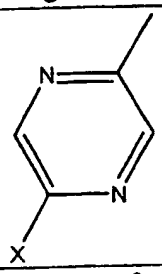
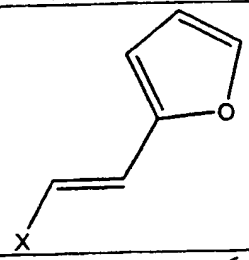
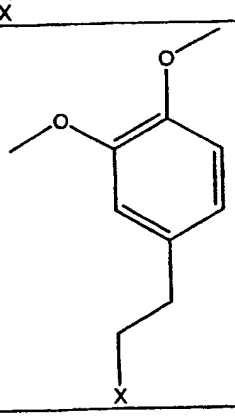
214		Z-GLY-GLY-GLY-GLY	1	1	2	2	1
215		Z-GLY-GLY-GLY	1	1	2	2	1
216		DELTA-VAL	1	1	2	1	1
217		D-ARG	2	3	3	2	1

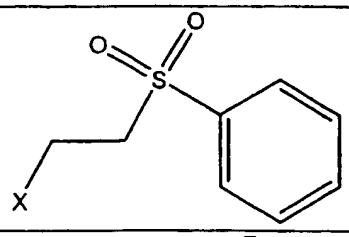
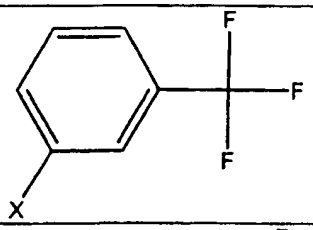
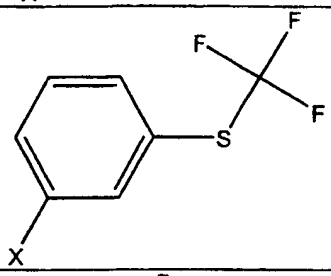
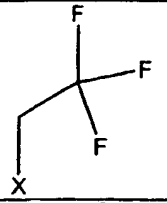
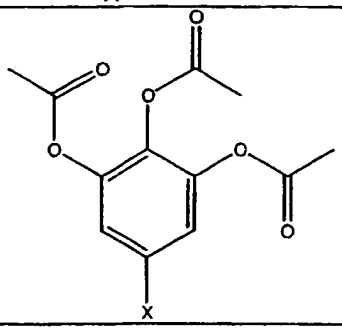
218		ACPC	1	1	2	1	1
219		DELTA-ABU	1	1	2	2	1
220		ALA	2	4	4	1	1
221		3-UREIDO PROPIONIC ACID	1	1	2	2	1
222		CARBOXY METHOXYL AMINE HEMIHYDRO CHLORIDE	1	1	2	2	1

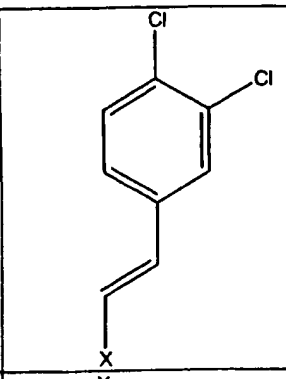
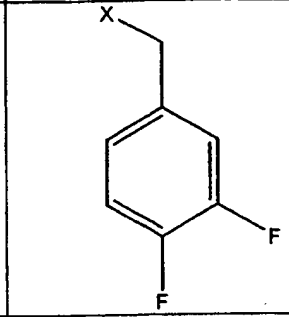
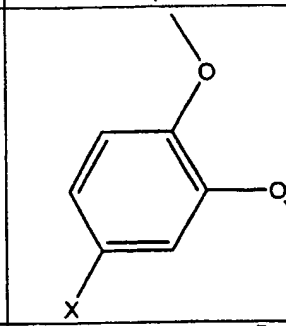
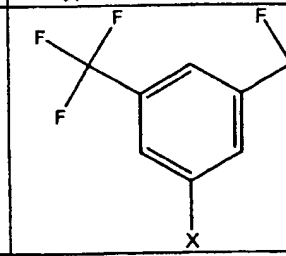
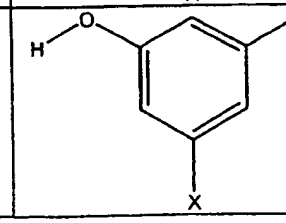
223		BOC-GLN-GLN-OH	1	1	2	2	1
224		(-)-2-OXO-4-THIAZOLIDINE-CARBOXYLIC ACID	1	2	2	2	1
225		(ETHYLTHIO) ACETIC ACID	1	3	4	2	1
226		(METHYLTHIO)ACETIC ACID	1	2	4	1	1
227		(R)-(-)-5-OXO-2-TETRAHYDRO FURAN CARBOXYLIC ACID	1	2	2	1	1
228		1H-TETRAZOLE-1-ACETIC ACID	1	2	1	2	1

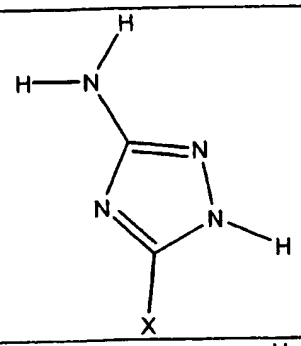
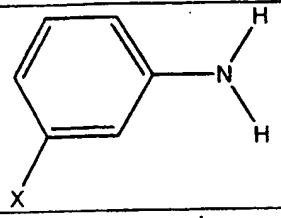
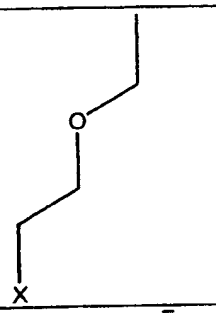
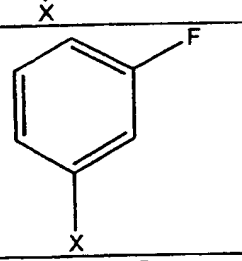
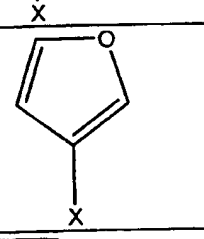
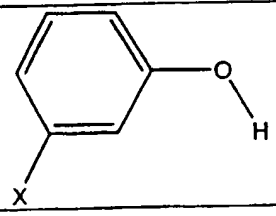
229		1-METHYL PYRROLE-2-CARBOXYLIC ACID	1	2	2	2	1
230		2-(4-CHLORO PHENYLTHIO) NICOTINIC ACID	1	1	2	2	1
231		2-(TRIFLUORO METHYL) PROPENOIC ACID	1	1	2	2	1
232		2,2-BIS(HYDROXY METHYL) PROPIONIC ACID	1	1	2	2	1
233		2,4,5-TRICHLORO PHENOXY ACETIC ACID	1	1	2	2	1
234		2,4-DICHLORO PHENYLACETIC ACID	1	2	2	2	1

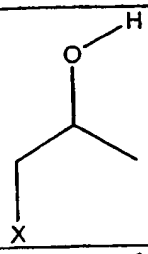
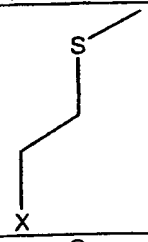
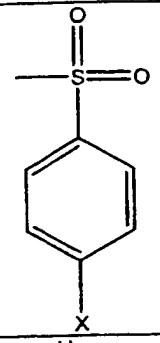
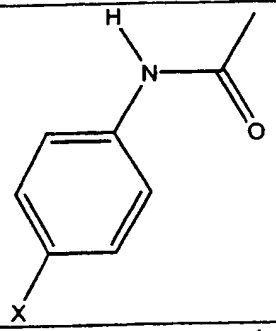
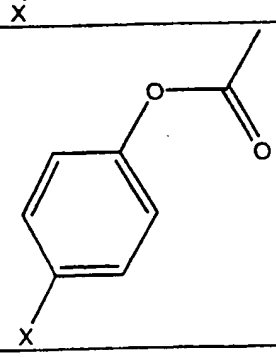
235		2,4-DIHYDROXY BENZOIC ACID	1	1	1	1	1
236		2,4-DIMETHOXY BENZOIC ACID	1	1	2	2	1
237		2-AMINO NICOTINIC ACID	1	2	4	2	1
238		2-FLUORO BENZOIC ACID	1	2	2	1	1
239		2-FURAN GLYOXYLIC ACID	1	1	2	1	1
240		2-FUROIC ACID	1	2	2	1	1

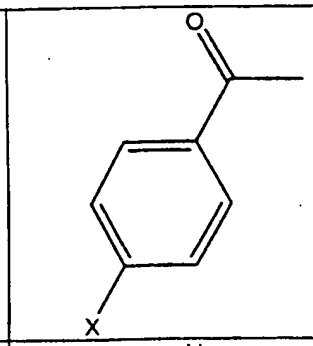
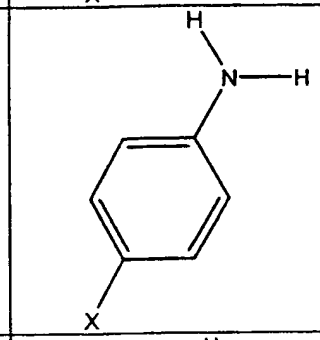
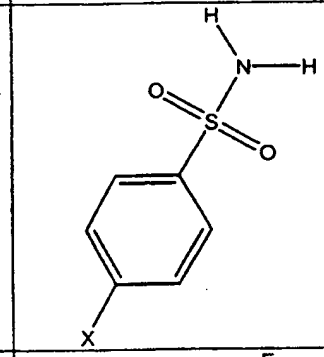
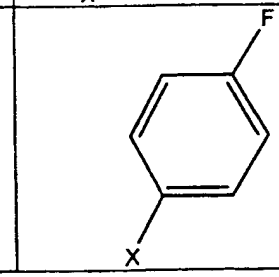
241		2-HYDROXY NICOTINIC ACID	1	1	1	2	1
242		2-KETOBUTYRIC ACID	1	1	1	2	1
243		2-METHYL PYRAZINE-5-CARBOXYLIC ACID	1	1	2	2	1
244		3-(2-FURYL) ACRYLIC ACID	1	2	2	3	1
245		3-(3,4-DIMETHOXYL PHENYL) PROPIONIC ACID	1	2	2	2	1

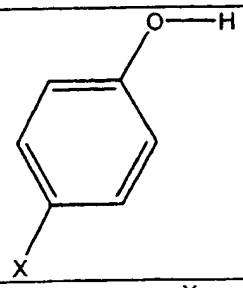
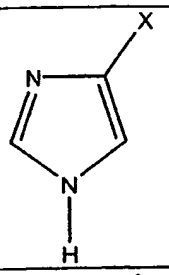
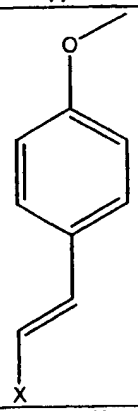
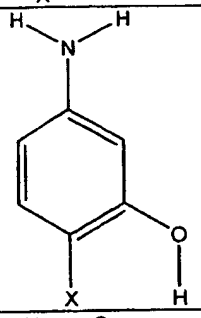
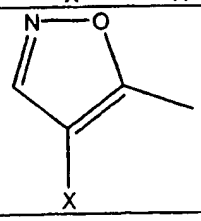
246		3-(PHENYL SULFONYL) PROPIONIC ACID	2	4	5	3	1
247		3-(TRIFLUORO METHYL) BENZOIC ACID	1	2	3	2	1
248		3-(TRIFLUORO METHYLTHIO) BENZOIC ACID	1	1	2	2	1
249		3,3,3-TRIFLUORO PROPIONIC ACID	1	3	4	2	1
250		3,4,5-TRIACETOXY BENZOIC ACID	1	2	3	1	1

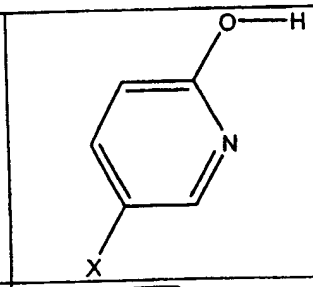
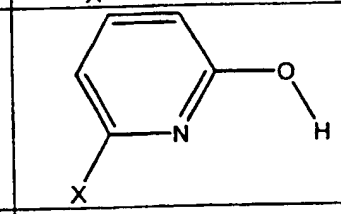
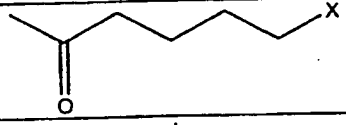
251		3,4-DICHLORO CINNAMIC ACID	1	1	1	2	1
252		3,4-DIFLUORO PHENYLACETIC ACID	1	2	4	1	1
253		3,4-DIMETHOXY BENZOIC ACID	1	2	2	2	1
254		3,5-BIS (TRIFLUORO METHYL) BENZOIC ACID	1	1	2	2	1
255		3,5-DIHYDROXY BENZOIC ACID	1	1	2	2	1

256		3-AMINO-1,2,4-TRIAZOLE-5-CARBOXYLIC ACID	1	1	2	2	1
257		3-AMINOBENZOIC ACID	1	2	2	2	1
258		3-ETHOXY PROPIONIC ACID	1	2	2	2	1
259		3-FLUORO BENZOIC ACID	1	2	3	1	1
260		3-FUROIC ACID	1	2	3	1	1
261		3-HYDROXY BENZOIC ACID	1	2	2	2	1

262		3-HYDROXY BUTYRIC ACID	1	2	2	2	1
263		3-METHYL THIOPROPIONIC ACID	1	4	5	1	1
264		4-(METHYL SULFONYL) BENZOIC ACID	1	2	2	0	1
265		4-ACETAMIDO BENZOIC ACID	1	1	2	2	1
266		4-ACETOXY BENZOIC ACID	1	2	2	2	1

267		4-ACETYL BENZOIC ACID	2	2	4	1	1
268		4-AMINO BENZOIC ACID	1	1	1	2	1
269		4-CARBOXY BENZENE SULFONAMIDE	1	2	2	2	1
270		4-FLUORO BENZOIC ACID	1	2	2	2	1

271		4-HYDROXY BENZOIC ACID	1	2	2	4	1
272		4-IMIDAZOLE CARBOXYLIC ACID	1	2	2	2	1
273		4-METHOXY CINNAMIC ACID	1	2	3	3	1
274		4-AMINO SALICYLIC ACID	1	2	2	2	1
275		5-METHYL ISOXAZOLE-4-CARBOXYLIC ACID	1	2	2	2	1

276		6-HYDROXY NICOTINIC ACID	1	2	3	1	1
277		6-HYDROXY PICOLINIC ACID	1	2	3	2	1
278		6-OXOHEPTANOIC ACID	1	1	2	2	1
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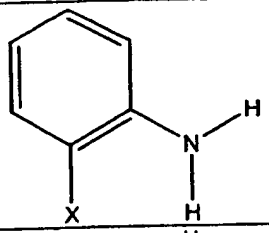
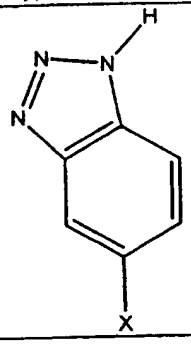
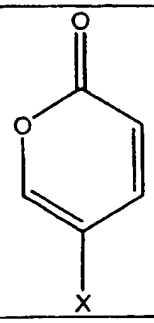
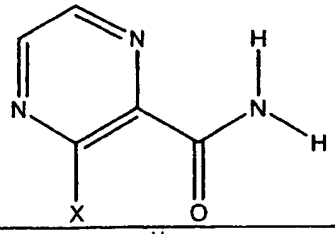
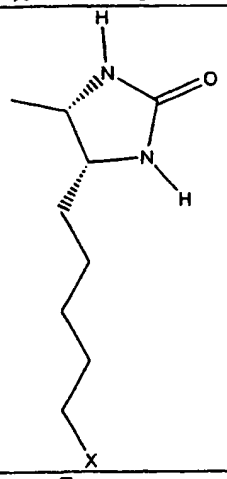
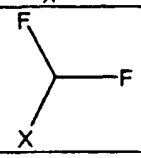
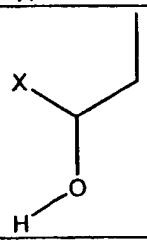
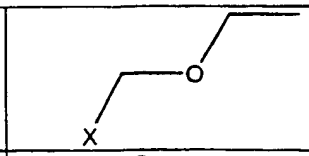
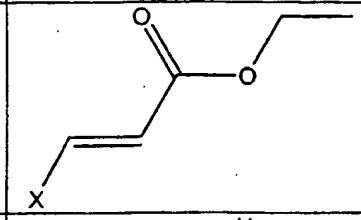
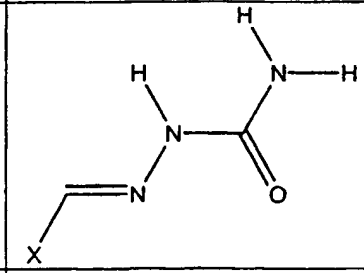
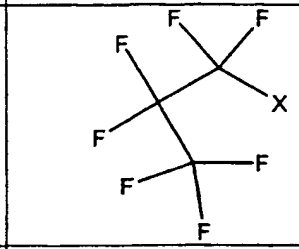
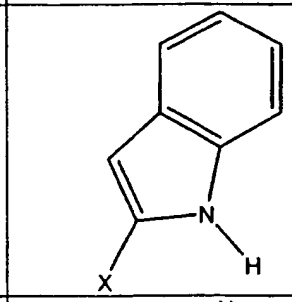
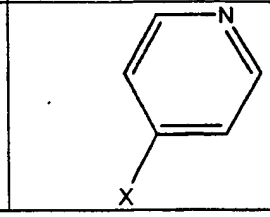
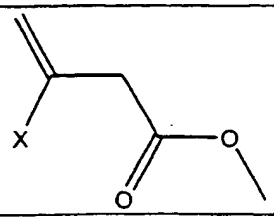
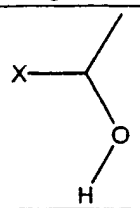
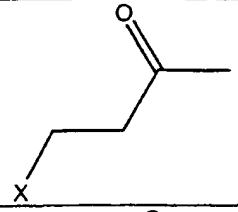
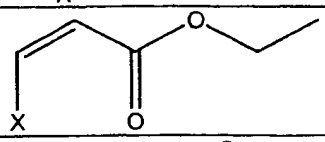
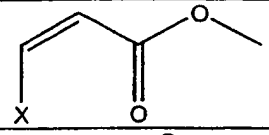
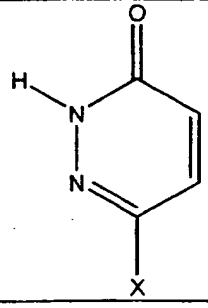
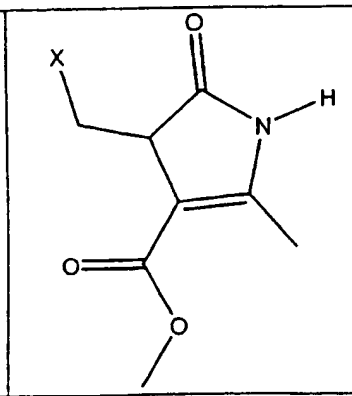
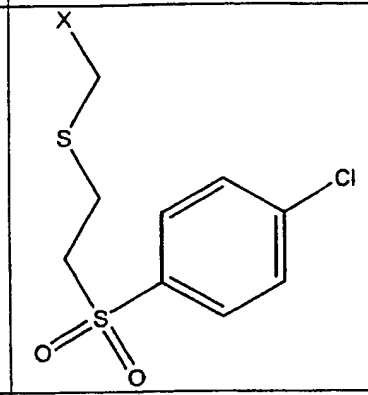
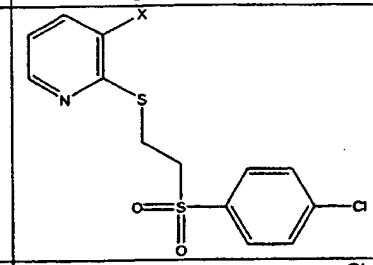
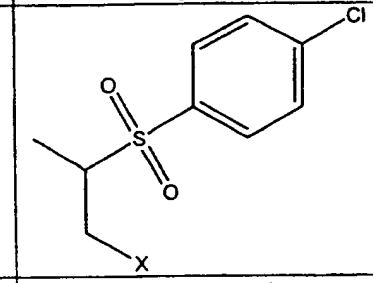
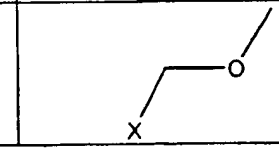
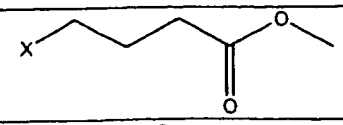
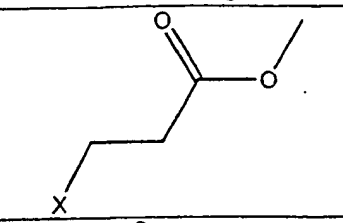
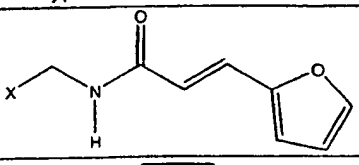
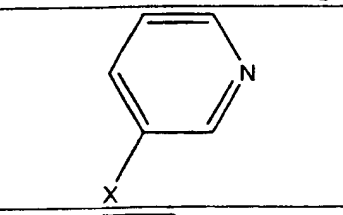
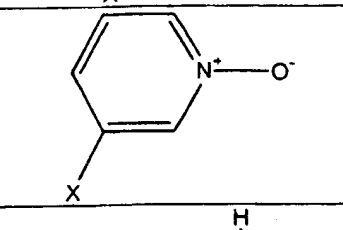
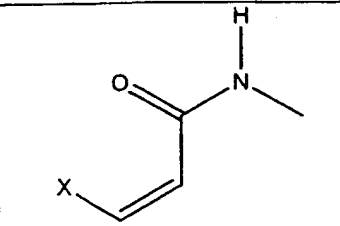
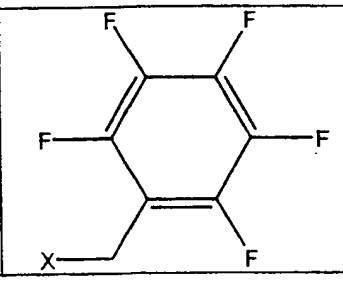
280		ANTHRANILIC ACID	1	2	3	2	1
281		BENZOTRIAZOLE-5-CARBOXYLIC ACID	1	2	2	2	1

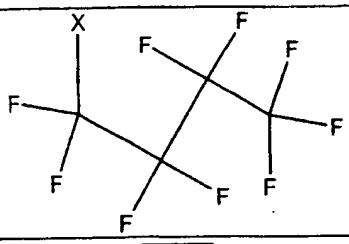
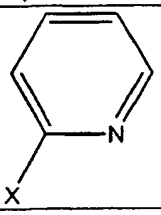
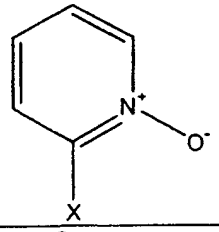
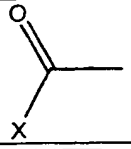
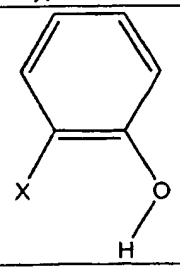
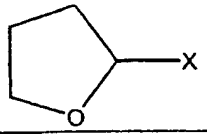
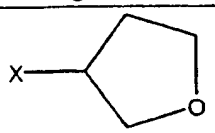
282		COUMALIC ACID	1	1	2	2	1
283		PYRAZINE-2,3-DICARBOXYLIC ACID MONOAMIDE	1	2	2	4	1
284		D-DESTHIO BIOTIN	1	2	3	2	1
285		DIFLUOROACETIC ACID	1	2	2	2	1
286		DL-2-HYDROXY-N-BUTYRIC ACID	1	2	2	2	1

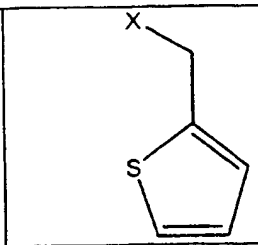
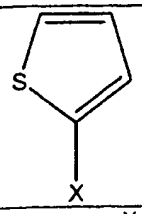
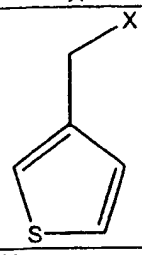
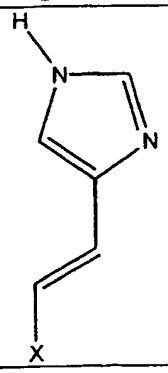
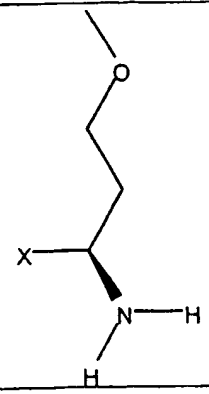
287		ETHOXYACETIC ACID	1	2	2	2	1
288		FUMARIC ACID MONETHYL ESTER	1	2	4	2	1
289		GLYOXYLIC ACID SEMICARBAZONE	1	2	2	1	1
290		HEPTAFLUORO BUTYRIC ACID	1	2	2	2	1
291		INDOLE-2-CARBOXYLIC ACID	1	2	2	2	1
292		ISONICOTINIC ACID	1	2	4	2	1

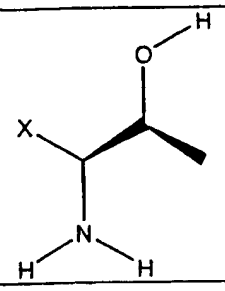
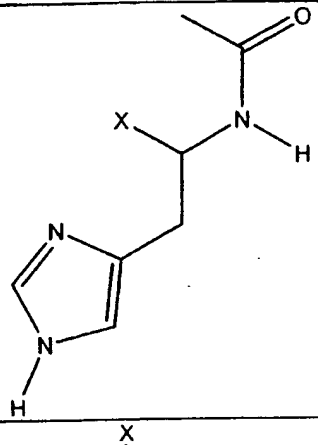
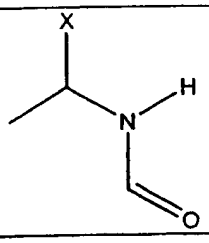
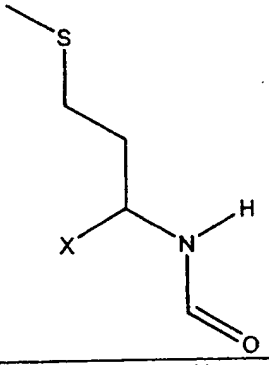
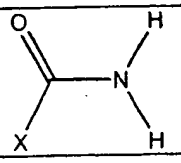
293		ITACONIC ACID MONOMETHYL ESTER	1	2	2	2	1
294		LACTIC ACID	1	2	3	2	1
295		LEVULINIC ACID	1	2	4	2	1
296		MALEIC ACID MONOETHYL ESTER	1	2	3	2	1
297		MALEIC ACID MONOMETHYL ESTER	1	1	2	2	1
298		2,3-DIHYDRO-3-OXOPYRIDAZINE-6-CARBOXYLIC ACID	1	1	2	2	1

299		MAYBRIDGE BTB 09316	1	1	2	4	1
300		MAYBRIDGE KM 01502	1	2	3	2	1
301		MAYBRIDGE KM 06000	1	2	2	2	1
302		3-(4-CHLORO BENZENE SULPHONYL) BUTYRIC ACID	1	3	4	3	1
303		METHOXYACETIC ACID	1	2	4	4	1

304		MONO-METHYL GLUTARATE	1	2	4	3	1
305		MOMO-METHYL SUCCINATE	1	2	4	3	1
306		N-[3-(2-FURYL ACRYLOYL)]-GLYCINE	1	2	3	2	1
307		NICOTINIC ACID	1	3	4	2	1
308		NICOTINIC ACID N-OXIDE	1	2	4	2	1
309		N0METHYL MALEAMIC ACID	1	2	3	2	1
310		PENTAFLUORO PHENYLACETIC ACID	1	2	4	2	1

311		PERFLUORO PENTANOIC ACID	1	1	2	1	1
312		PICOLINIC ACID	1	2	2	2	1
313		PICOLINIC ACID N-OXIDE	1	2	2	2	1
314		PYRUVIC ACID	1	2	2	2	1
315		SALICYLIC ACID	1	1	1	2	1
316		TETRAHYDRO-2-FUROIC ACID	1	2	2	3	1
317		TETRAHYDRO-3-FUROIC ACID	1	3	4	2	1

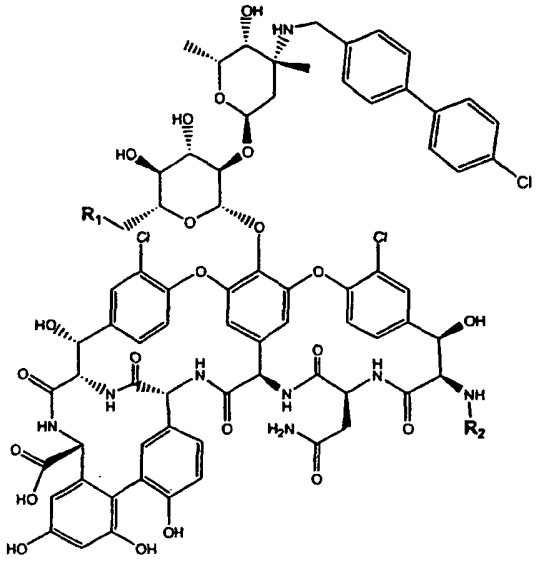
318		THIOPHENE-2-ACETIC ACID	1	2	4	3	1
319		THIOPHENE-2-CARBOXYLIC ACID	1	2	3	2	1
320		THIOPHENE-3-ACETIC ACID	1	2	3	2	1
321		UROCANIC ACID	1	2	2	2	1
322		HSE(ME)	1	2	2	2	1

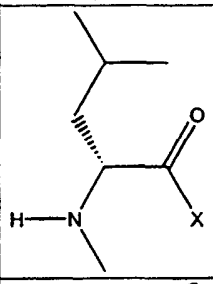
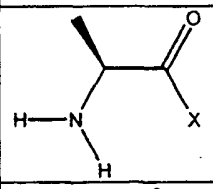
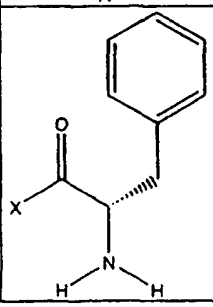
323		L-THREONINE MONOHYDRATE	1	2	2	2	1
324		N-ACETYL-DL-HISTIDINE HYDRATE	1	2	2	2	1
325		N-FORMYL-DL-ALANINE	1	2	3	2	1
326		N-FORMYL-DL-METHIONINE	1	2	2	2	1
327		OXAMIC ACID	1	2	3	3	1

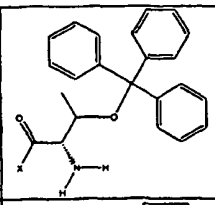
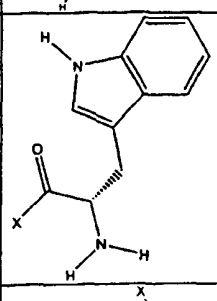
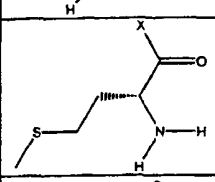
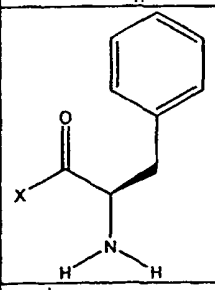
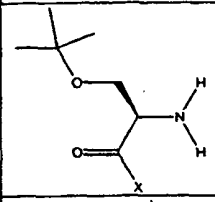
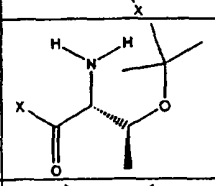
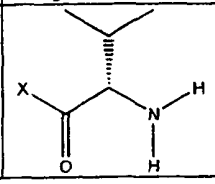
In Table II, below, MIC (minimum inhibitory concentration) values of certain compounds of the present invention are provided for the bacterial strains *E. faecium* ATCC 49624, *E. faecium* CL 4931, *E. faecalis* ATCC 29212, *E. Faecalis* CL 4877, *S aureus* ATCC 29213, and *S. Aureus* ATCC 33591. The minimum inhibitory concentrations (MIC) of test compounds were determined using bacteria grown in brain heart infusion media (BHI) supplemented with 0.1% casamino acids. Logarithmically growing cells were diluted to approximately 5 X 10^5 CFU/ml and subjected to test compounds solubilized and serially diluted in DMSO. A 5% final DMSO concentration had no affect on cell viability or killing. After 18 hours at 37°C, the OD_{600} was determined by reading the ninety-six well microtiter plates on a microplate reader. For a given concentration, an MIC determination was made if:

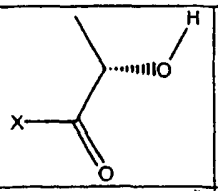
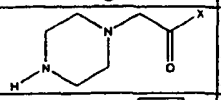
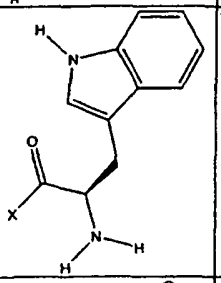
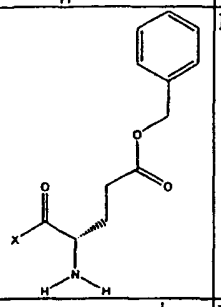
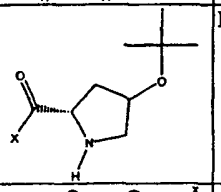
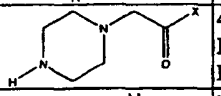
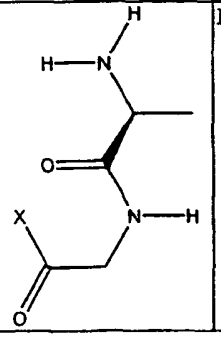
$[OD_{600}$ Control – OD_{600} Test Conc.$]/[OD_{600}$ Control – OD_{600} Media$] \times 100 \geq 90\%$

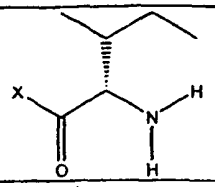
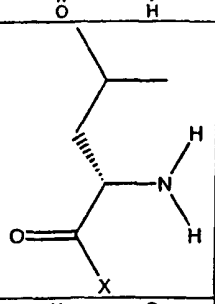
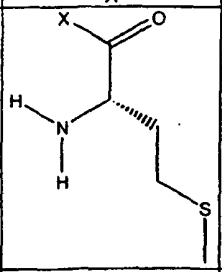
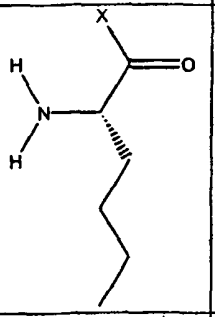
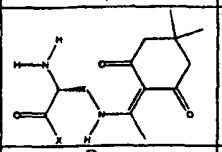
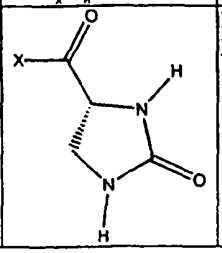
Table II MIC Values of Compounds of the Invention Against Selected Baterial Strains

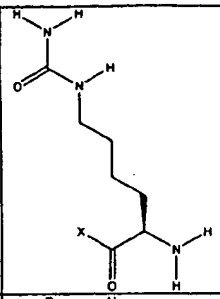
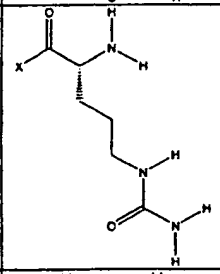
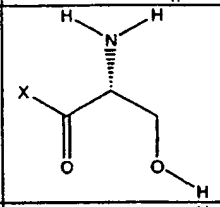
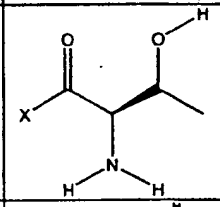
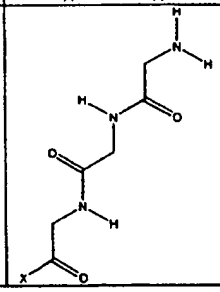


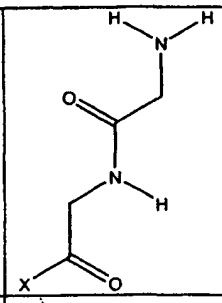
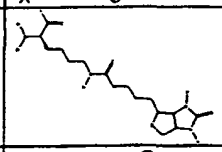
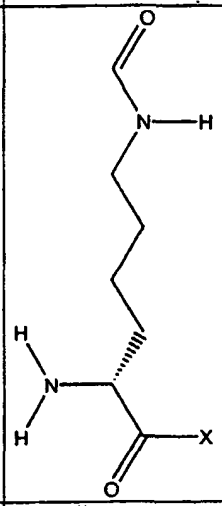
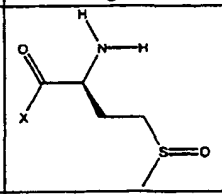
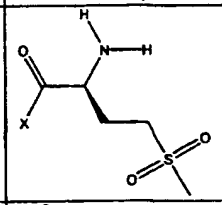
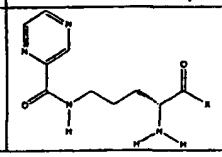
Cmpd No.	R1	R2	Reagent Name	*E. faecium ATCC 49624*	*E. faecium CL 4931*	*E. faecalis ATCC 29212*	*E. faecalis CL 4877*	*S. aureus ATCC 29213*	*S. aureus ATCC 33591*
0	OH		Vancomycin (Vancosamine sugar is unsubstituted in this compound only.)	1.25	>250	3.12	>250	1.25	2.5
1	OH		L-ALA	0.78	25	1.56	25	0.78	0.78
7	OH		L-PHE	0.12	6.25	0.78	6.25	0.39	0.39

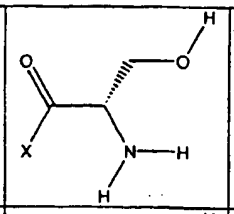
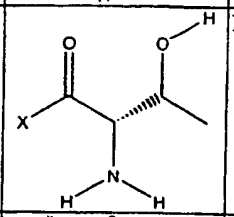
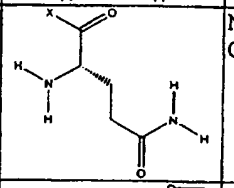
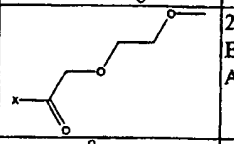
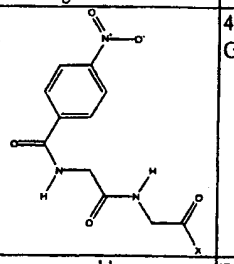
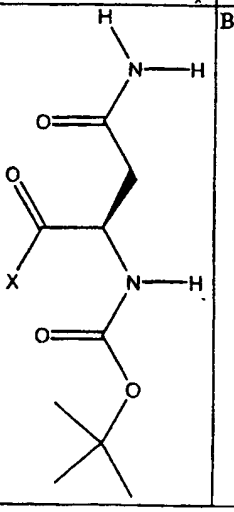
11	OH		L-THR(TRT)	3.12	6.25	3.12	3.12	3.12	3.12
12	OH		L-TRP	0.39	6.25	1.56	3.12	0.78	0.78
15	OH		D-MET	0.12	12.5	0.25	12.5	0.25	0.12
16	OH		D-PHE	0.12	12.5	0.25	12.5	0.25	0.25
17	OH		D-SER(TBU)	0.062	6.25	0.25	3.91	0.062	0.12
18	OH		D-THR(TBU)	0.25	25	1.56	25	0.78	0.78
20	OH		L-VAL	0.25	12.5	0.78	3.12	0.25	0.39

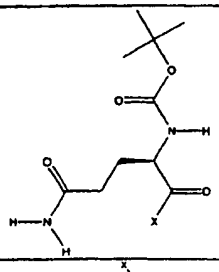
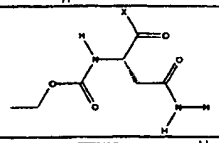
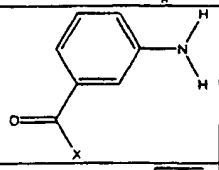
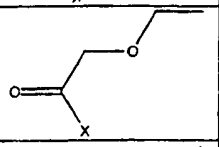
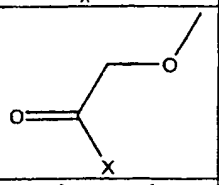
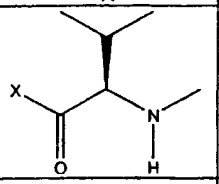
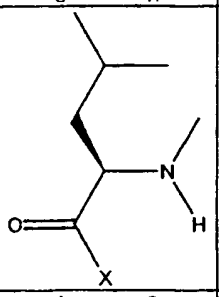
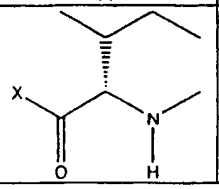
21	OH		L-(+)-LACTIC ACID	3.12	25	6.25	25	1.56	3.12
24	OH		PIPERAZIN-1-YL ACETIC ACID HYDRATE	1.56	25	1.56	6.25	0.78	0.78
25	OH		D-TRP	0.25	12.5	0.39	6.25	0.25	0.25
26	OH		L-GLU(OBZL)	1.56	>25	1.56	12.5	0.78	0.78
30	OH		L-HYP(TBU)	0.78	25	3.12	25	1.56	1.56
34	OH		4-CARBOXY METHYL-PIPERAZINE	0.78	25	3.12	6.25	0.78	1.56
36	OH		L-ALA-GLY	0.12	12.5	0.78	6.25	0.39	0.39

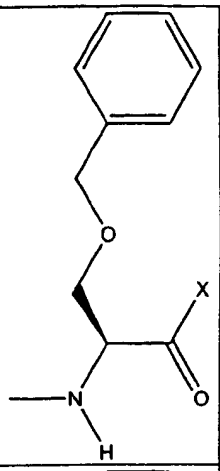
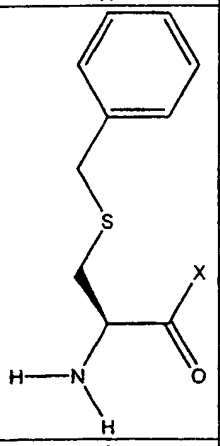
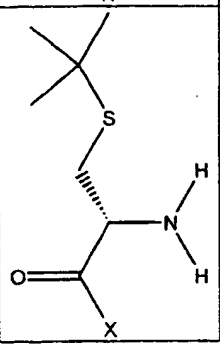
37	OH		L-ILE	0.25	12.5	0.78	3.12	0.39	0.39
38	OH		L-LEU	0.78	12.5	1.56	12.5	0.78	0.78
41	OH		L-MET	0.25	12.5	0.78	12.5	0.39	0.39
42	OH		L-NLE	0.39	12.5	0.78	6.25	0.39	0.39
56	OH		D-DPR(DDE)	0.12	12.5	0.78	12.5	0.25	0.25
56-3	OH		D-DPR(DDE) Deprotect/Rearrange	0.12	6.25	0.25	6.25	0.25	0.25

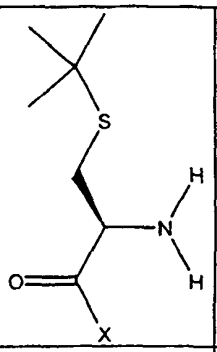
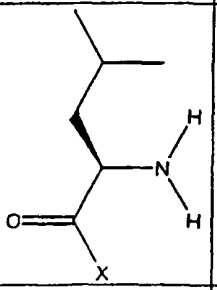
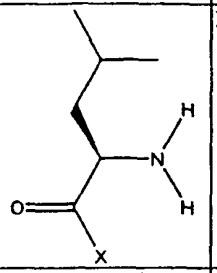
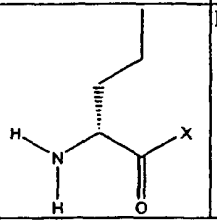
61	OH		D-LYS (CARBAMYL)	0.12	12.5	0.25	12.5	0.12	0.12
62	OH		D-ORN (CARBAMYL)	0.12	12.5	0.25	12.5	0.25	0.25
63	OH		D-SER	0.78	25	1.56	12.5	0.78	0.78
64	OH		D-THR	0.39	25	1.56	12.5	0.78	0.78
67	OH		GLY-GLY-GLY	0.78	12.5	1.56	6.25	0.78	0.78

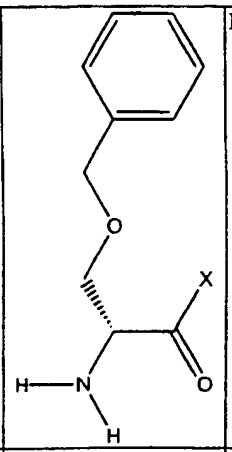
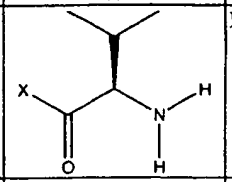
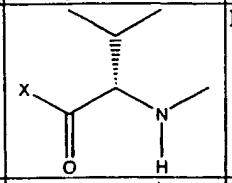
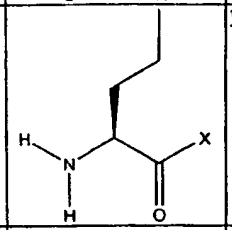
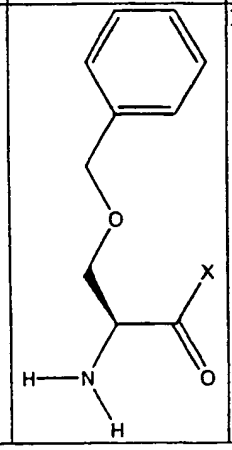
68	OH		GLY-GLY	0.39	12.5	1.56	6.25	0.78	0.78
75	OH		L-LYS(BIOTIN)	0.39	25	3.12	25	1.56	1.56
79	OH		L-LYS(FOR)	0.78	25	3.12	25	1.56	1.56
81	OH		L-MET(O)	0.78	25	1.56	25	0.78	1.56
82	OH		L-MET(O2)	0.39	25	1.56	12.5	0.78	0.78
83	OH		L-ORN(PYRAZINYL CARBONYL)	0.25	25	0.78	12.5	0.39	0.78

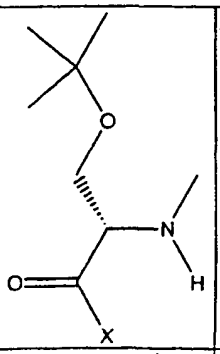
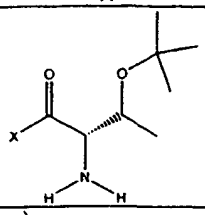
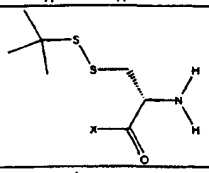
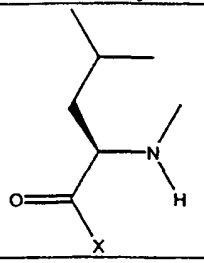
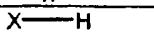
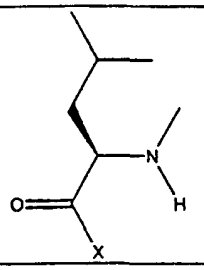
88	OH		L-SER	0.78	12.5	1.56	25	0.78	1.56
89	OH		L-THR	0.78	>25	3.12	12.5	1.56	1.56
91	OH		N-ALPHA- L-GLUTAMINE	0.78	25	1.56	12.5	0.78	0.78
100	OH		2-(2-METHOXY ETHOXY) ACETIC ACID	0.78	6.25	1.56	6.25	0.25	0.78
108	OH		4-NITROBENZOYL-GLYCYL-GLYCINE	1.56	>25	3.12	>25	0.78	0.78
135	OH		BOC-D-ASN	0.39	>25	3.12	12.5	1.56	1.56

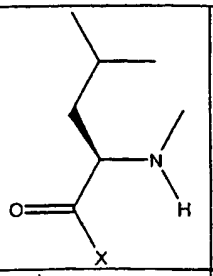
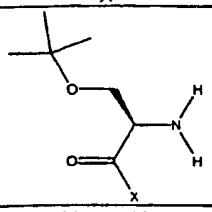
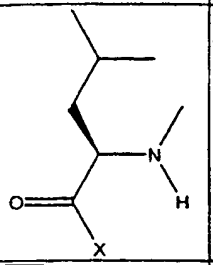
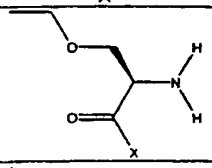
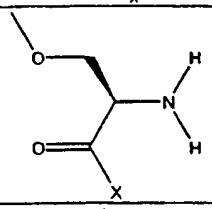
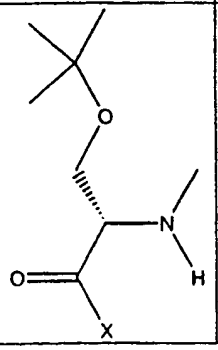
136	OH		BOC-D-GLN	0.78	>25	1.56	12.5	0.78	0.78
188	OH		N-ALPHA-CARBOETHOXY-L-ASPARAGINE	0.062	6.25	0.39	3.12	0.39	0.39
257	OH		3-AMINOBENZOIC ACID	0.39	25	1.56	12.5	0.78	0.78
287	OH		ETHOXYACETIC ACID	1.56	25	3.12	12.5	1.56	3.12
303	OH		METHOXYACETIC ACID	1.56	25	3.12	12.5	1.56	1.56
328	OH		D-ME-VAL	0.12	12.5	0.39	12.5	0.25	0.25
329	OH		D-ME-LEU	0.031	6.25	0.12	6.25	0.25	0.12
330	OH		L-ME-ILE	0.12	12.5	0.78	3.12	0.25	0.25

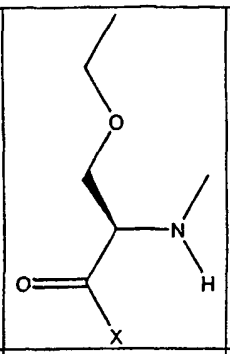
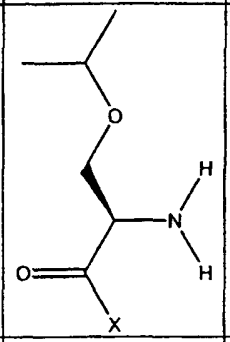
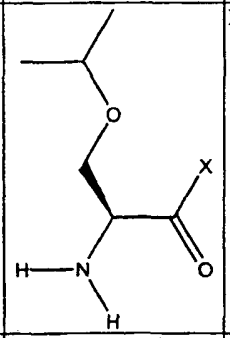
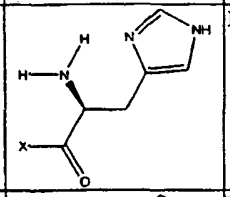
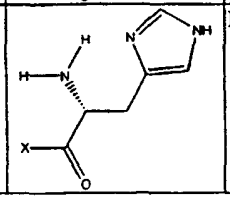
331	OH		L-ME-SER(BZL)	0.39	12.5	1.56	6.25	0.78	0.78
332	OH		L-CYS(BZL)	1.56	25	3.12	12.5	1.56	1.56
333	OH		L-CYS(TBU)	1.56	25	3.12	25	1.56	1.56

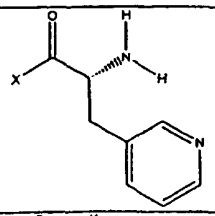
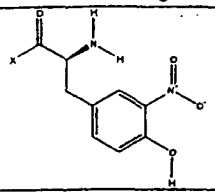
334	OH		D-CYS(TBU)	0.12	25	0.78	12.5	0.25	0.25
335	OH		D-ILE	0.12	12.5	0.39	12.5	0.12	0.25
336	OH		D-LEU	0.12	6.25	0.25	12.5	0.25	0.25
337	OH		D-NVA	0.062	12.5	0.25	12.5	0.12	0.12

338	OH		D-SER(BZL)	0.25	12.5	1.56	25	1.56	0.39
339	OH		D-VAL	0.12	12.5	0.25	12.5	0.25	0.25
340	OH		L-ME-VAL	0.39	12.5	1.56	25	0.39	0.39
341	OH		L-NVA	0.78	12.5	1.56	25	0.78	0.78
342	OH		L-SER(BZL)	0.39	25	1.56	12.5	0.78	0.78

343	OH		L-SER(TBU)	0.39	25	3.12	12.5	1.56	0.78
344	OH		L-THR(TBU)	0.78	25	3.12	12.5	1.56	1.56
345	OH		L-CYS(STBU)	0.39	25	3.12	12.5	0.78	0.78
517	OH		TS0517 (Cl-Biphenyl Vancomycin)	0.062	12.5	0.25	12.5	0.25	0.25
518	OH		TS0518 (Des-Lecyl Cl-Biphenyl Vanc)	1.56	12.5	3.12	25	3.12	6.25
519	I		6'-Deoxy-6'-Iodo	0.78	>25	3.12	>25	1.56	3.12

520	I		6'-Deoxy-6'-Iodo-ChloroBiphenyl	0.12	12.5	0.78	12.5	0.78	0.78
521	NH2		6'-Deoxy-6'-Amino TS1017	0.12	12.5	0.78	6.25	0.78	0.78
522	OH		Des-Lecyl Vancomycin	>25	>25	>25	>25	>25	>25
523	NH2		6'-Deoxy-6'-Amino TS0517	0.12	6.25	0.25	6.25	0.78	0.39
524	OH		D-SER(ET)	0.25	25	1.56	12.5	0.39	0.39
525	OH		D-SER(ME)	0.25	25	1.56	25	0.39	0.39
526	OH		N-Methyl-L-SER(TBU)	0.25	25	0.78	6.25	0.39	0.39

527	OH		N-Methyl-D-SER(ET)	0.25	25	1.56	12.5	0.39	0.39
528	OH		D-SER(ISOPROPYL)	0.12	25	0.78	12.5	0.25	0.25
529	OH		L-SER(ISOPROPYL)	0.12	25	0.78	12.5	0.25	0.25
554	OH		L-HIS	0.39	12.5	3.12	25	1.56	0.78
555	OH		D-HIS	0.39	12.5	1.56	12.5	0.78	0.39

556	OH		D-GLY-(2-Pyridyl)	0.39	25	0.78	25	0.78	0.39
557	OH		L-Phe-(3-Nitro-2-Hydroxy)	0.39	25	1.56	25	1.56	1.56

WHAT IS CLAIMED IS:

1. A compound having the formula A_1-A_2-A_3-A_4-A_5-A_6-A_7 wherein each of the groups A_2 to A_7 comprises a modified or unmodified α-amino acid residue, A_1 is optional and, when present, comprises an organic group other than N-substituted leucine, and at least one of the groups A_1 to A_7 is linked via a glycosidic bond to one or more glycosidic groups each having one or more sugar residues, wherein at least one of said sugar residues is modified to bear at least one hydrophobic substituent.

2. The compound of claim 1 wherein said glycosidic group is a disaccharide modified to bear said at least one hydrophobic substituent.

3. The compound of claim 1 wherein each of the groups A_2, A_4, A_5, A_6 and A_7 bears an aromatic side chain and the aromatic side chains of groups A_2 and A_6 are linked to the aromatic side chain of group A_4 via ether linkages and the aromatic side chains of groups A_5 and A_7 are linked to each other via a carbon-carbon bond.

4. The compound of claim 3 wherein the group A_4 is linked to a glycosidic group modified to bear said at least one hydrophobic substituent.

5. The compound of claim 4 wherein said glycosidic group is a disaccharide comprising a glucose residue directly bonded to group A_4 and a vancosamine residue bonded to said glucose residue.

6. The compound of claim 5 wherein A_2-A_3-A_4-A_5-A_6-A_7 is as found in a compound selected from the group consisting of vancomycin, eremomycin, chloroeremomycin, and β-avoparcin.

7. The compound of claim 6 wherein A_2-A_3-A_4-A_5-A_6-A_7 is as found in vancomycin.

8. The compound of claim 7 wherein the C_6 position of said glucose residue is modified to bear

at least one substituent other than hydroxyl.

9. The compound of claim 8 wherein said at least one substituent other than hydroxyl is a polar substituent.

10. The compound of claim 8 wherein said at least substituent other than hydroxyl is a hydrophobic substituent.

11. The compound of claim 7 wherein the vancosamine residue in vancomycin is N-substituted with said at least one hydrophobic substituent.

12. The compound of claim 7 wherein said glucose residue is modified to bear at least one substituent other than hydroxyl and said vancosamine residue is N-substituted with said at least one hydrophobic substituent.

13. The compound of claim 12 wherein said at least one substituent other than hydroxyl is a polar substituent.

14. The compound of claim 1 wherein said at least one hydrophobic substituent is R, OR, NR_1R, SR, SO_2R, C(O)OR, C(O)SR, C(S)OR, C(S)SR, $NR_1C(O)R$, $C(O)NR_1R$, or halo and R is alkyl, aryl, aralkyl, alkanoyl, aroyl, aralkanoyl, heterocyclic, heterocyclic-carbonyl, heterocyclic-alkyl, heterocyclic-alkyl-carbonyl, alkylsulfonyl or arylsulfonyl; R_1 is hydrogen, alkyl, aryl, aralkyl, alkanoyl, aroyl, aralkanoyl, heterocyclic, heterocyclic-carbonyl, heterocyclic-alkyl, heterocyclic-alkyl-carbonyl, alkylsulfonyl or arylsulfonyl; and any pharmaceutically acceptable salts thereof; and if two or more of said substituents are present, they can be the same or different.

15. The compound of claim 1 wherein said organic group is selected from the group consisting of a modified or unmodified alpha amino acid residue, alkyl, aryl, aralkyl, alkanoyl, aroyl, aralkanoyl, heterocyclic, heterocyclic-carbonyl, heterocyclic-alkyl, heterocyclic-alkyl-carbonyl, alkylsulfonyl, arylsulfonyl, guanidinyl, carbamoyl, or xanthyl.

16. The compound of claim 1 wherein the group A_7 bears a terminal carboxyl, ester, thioester, amide, N-substituted amide, or other carboxylic acid derivative.

17. A method for making a compound of the formula A_1-A_2-A_3-A_4-A_5-A_6-A_7 wherein each of the groups A_2 to A_7 comprises a modified or unmodified α-amino acid residue, A_1 comprises an organic group other than N-substituted leucine, and at least one of the groups A_1 to A_7 is linked via a glycosidic bond to one or more glycosidic groups each having one or more sugar residues, wherein at least one of said sugar residues is modified to bear at least one hydrophobic substituent, said method comprising

removing the N-substituted leucine residue from the compound N-substituted-leucyl-A_2-A_3-A_4-A_5-A_6-A_7 thereby forming a compound having a free amino group at A_2; and

attaching an organic group A_1 to the free amino group at A_2.

18. The method of claim 17 wherein the N-substituted leucine residue is N-methyl leucine.

19. The method of claim 17 wherein said glycosidic group is a disaccharide modified to bear said at least one hydrophobic substituent.

20. The method of claim 17 wherein each of the groups A_2, A_4, A_5, A_6 and A_7 bears an aromatic side chain and the aromatic side chains of groups A_2 and A_6 are linked to the aromatic side chain of group A_4 via ether linkages and the aromatic side chains of groups A_5 and A_7 are linked to each other via a carbon-carbon bond.

21. The method of claim 20 wherein the group A_4 is linked to a glycosidic group modified to bear said at least one hydrophobic substituent.

22. The method of claim 21 wherein said glycosidic group is a disaccharide comprising a glucose residue directly bonded to group A_4 and a vancosamine residue bonded to said glucose residue.

23. The method of claim 22 wherein A_2-A_3-A_4-A_5-A_6-A_7 is as found in a compound selected from the group consisting of vancomycin, eremomycin, chloroeremomycin, and β-avoparcin.

24. The method of claim 23 wherein A_2-A_3-A_4-A_5-A_6-A_7 is as found in vancomycin.

25. The method of claim 24 wherein the C_6 position of said glucose residue is modified to bear at least one substituent other than hydroxyl.

26. The method of claim 25 wherein said at least one substituent other than hydroxyl is a polar substituent.

27. The method of claim 25 wherein said at least substituent other than hydroxyl is a hydrophobic substituent.

28. The method of claim 24 wherein the vancosamine residue in vancomycin is N-substituted with said least one hydrophobic substituent.

29. The method of claim 24 wherein said glucose residue is modified to bear at least one substituent other than hydroxyl and said vancosamine residue is N-substituted with said least one hydrophobic substituent.

30. The method of claim 29 wherein said substituent other than hydroxyl is a polar substituent.

31. The method of claim 17 wherein said at least one hydrophobic substituent is R, OR, NR_1R, SR, SO_2R, C(O)OR, C(O)SR, C(S)OR, C(S)SR, $NR_1C(O)R$, $C(O)NR_1R$, or halo and R is alkyl, aryl, aralkyl, alkanoyl, aroyl, aralkanoyl, heterocyclic, heterocyclic-carbonyl, heterocyclic-alkyl, heterocyclic-alkyl-carbonyl, alkylsulfonyl or arylsulfonyl; R_1 is hydrogen, alkyl, aryl, aralkyl, alkanoyl, aroyl, aralkanoyl, heterocyclic, heterocyclic-carbonyl, heterocyclic-alkyl, heterocyclic-alkyl-carbonyl, alkylsulfonyl or arylsulfonyl; and any pharmaceutically acceptable salts thereof;

and if two or more of said substituents are present, they can be the same or different.

32. The method of claim 17 wherein said organic group is selected from the group consisting of a modified or unmodified alpha amino acid residue, alkyl, aryl, aralkyl, alkanoyl, aroyl, aralkanoyl, heterocyclic, heterocyclic-carbonyl, heterocyclic-alkyl, heterocyclic-alkyl-carbonyl, alkylsulfonyl, arylsulfonyl, guanidinyl, carbamoyl, or xanthyl.

33. The method of claim 17 wherein the group A_7 bears a terminal carboxyl, ester, thioester, amide, N-substituted amide, or other carboxylic acid derivative.

34. A method for making a glycopeptide antibiotic having the formula A_1-A_2-A_3-A_4-A_5-A_6-A_7 wherein A_2-A_3-A_4-A_5-A_6-A_7 is as found in vancomycin and A_1 comprises an organic group other than N-substituted leucine, said method comprising

modifying vancomycin to form a modified vancomycin bearing a hydrophobic substituent at the vancosamine nitrogen;

removing the N-methyl leucine residue from the modified vancomycin to form a des-N-methyl leucyl modified vancomycin bearing a free amino group at A_2; and

attaching an organic group A_1 to the amino group at A_2.

35. The method of claim 34 wherein said organic group is selected from the group consisting of a modified or unmodified alpha amino acid residue, alkyl, aryl, aralkyl, alkanoyl, aroyl, aralkanoyl, heterocyclic, heterocyclic-carbonyl, heterocyclic-alkyl, heterocyclic-alkyl-carbonyl, alkylsulfonyl, arylsulfonyl, guanidinyl, carbamoyl, or xanthyl.

36. A method for making a glycopeptide antibiotic having the formula A_1-A_2-A_3-A_4-A_5-A_6-A_7 wherein A_2-A_3-A_4-A_5-A_6-A_7 is as found in vancomycin and A_1 comprises an organic group other than N-substituted leucine, said method comprising

modifying vancomycin to form a first modified vancomycin bearing a substituent other than hydroxyl at the C_6 position of the glucose attached to A_4 of vancomycin;

modifying said first modified vancomycin to form a second modified vancomycin bearing a hydrophobic substituent at the vancosamine nitrogen;

removing the N-methyl leucine residue from said second modified vancomycin to form a des-N-methyl leucyl second modified vancomycin bearing a free amino group at A_2; and,

attaching an organic group A_1 to the amino group at A_2.

37. The method of claim 36 wherein said substituent other than hydroxyl is a polar substituent.

38. The method of claim 36 wherein said organic group is selected from the group consisting of a modified or unmodified alpha amino acid residue, alkyl, aryl, aralkyl, alkanoyl, aroyl, aralkanoyl, heterocyclic, heterocyclic-carbonyl, heterocyclic-alkyl, heterocyclic-alkyl-carbonyl, alkylsulfonyl, arylsulfonyl, guanidinyl, carbamoyl, or xanthyl.

39. A method for removing an N-terminal amino acid residue from an oligopeptide or polypeptide comprising reacting an oligopeptide or a polypeptide with phenylisothiocyanate in a pyridine-water-triethylamine solvent medium.

40. The method of claim 39 wherein the reaction is carried out in a 10:10:1 pyridine-water-triethylamine solvent medium.

41. The method of claim 39 wherein the reaction is carried out at a temperature in the range of from 40 – 70 C.

42. The method of claim 39 wherein the reaction is carried out for period of time in the range of from 20 – 60 minutes.

43. The method of claim 39 wherein the N-terminal amino acid residue is N-methyl leucine.

44. The method of claim 43 wherein the oligopeptide is selected from the group consisting of a glycopeptide antibiotic, a pseudoaglycone and an aglycone.

45. The method of claim 43 wherein the oligopeptide is a glycopeptide antibiotic or

pseudoaglycone in which at least one glycosidic groups therein is modified to bear at least one hydrophobic substituent.

46. The method of claim 45 wherein the glycopeptide antibiotic is vancomycin.

47. The method of claim 46 wherein the disaccharide at A_4 of vancomycin is modified to bear at least one hydrophobic group.

48. The method of claim 47 wherein the vancosamine nitrogen at A_4 of vancomycin is modified to bear at least one hydrophobic group.

49. The method of claim 47 wherein the glucose residue attached directly to A_4 of vancomycin is modified to bear at least one substituent other than hydroxyl.

50. The method of claim 49 wherein said at least one hydrophobic substituent other than hydroxyl is a polar substituent or a hydrophobic substituent.

51. The method of claim 50 wherein the C_6 position of said glucose residue attached directly to A_4 of vancomycin is modified to bear a polar or a hydrophobic substituent.

52. A method of treating an infectious disease in a host comprising administering to said host an effective amount of a compound of claim 1 or a pharmaceutically acceptable salt or ester thereof.

53. The method of claim 52 wherein the host is a mammal.

54. The method of claim 53 where the mammal is a human.

55. The method of claim 52 wherein the infectious disease is a bacterial infection.

56. The method of claim 52 further comprising administering to said host an additional drug or

therapeutic agent in combination with a compound of claim 1 or a pharmaceutically acceptable salt or ester thereof.

57. A composition comprising a compound of claim 1 or a pharmaceutically acceptable salt or ester thereof and a pharmaceutically acceptable carrier or excipient.

58. The composition of claim 57 further comprising an additional drug or therapeutic agent.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US00/08559

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) :A61K 38/08, 38/14; C07K 1/07, 7/06, 9/00

US CL :436/89, 90; 514/7, 8, 9, 10, 11, 16, 17; 530/322, 343, 345

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 436/89, 90; 514/7, 8, 9, 10, 11, 16, 17; 530/322, 343, 345

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

Please See Extra Sheet.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 97/02288 A1 (GRUPPO LEPETIT S.P.A.) 23 January 1997 (23/01/97), page 7, lines 4-10 and 16-35, page 9, lines 1-28, page 24, lines 4-22.	1, 3, 4, 14-16, 52-58
X,P --- Y,P	WO 99/56760 A1 (ELI LILLY AND COMPANY) 11 November 1999 (11.11.99), page 1, line 10 - page 3, line 17, page 5, line 7 - page 6, line 14, page 7, line 15 - page 8, line 7, claims 3-5.	1-7, 11, 14-24, 28, 31-35, 52-58 --- 39-48
X --- Y	US 4,791,100 A (KRAMER ET AL) 13 December 1988 (13/12/88), column 6, lines 31-38.	39-42 --- 39-48
A,P	US 5,977,063 A (THOMPSON ET AL) 02 November 1999 (02/11/99).	1-58

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search 30 MAY 2000	Date of mailing of the international search report 13 JUL 2000
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer JEFFREY E. RUSSEL Telephone No. (703) 308-0196

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US00/08559

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 4,643,987 A (NAGARAJAN ET AL) 17 February 1987 (17/02/87), Table I, Compound No. 17, column 9, lines 1-59.	1-7, 11, 14-16, 52-58

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US00/08559

B. FIELDS SEARCHED
Electronic data bases consulted (Name of data base and where practicable terms used):

WEST, DERWENT, DIALOG
search terms: glycopeptide, vancomycin, dalbaheptide, eremomycin, chloroeremomycin, avoparcin, vancosamine, conjugate, hydrophobic, lipophilic, acylate, fatty acid, lipoglycopeptide, edman, phenylisothiocyanate, pyridine, triethylamine